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CONTENTS

Simple Tests of Ventilatory Function for Use in the Sanatorium or Clinic. FREDERICK C. WARRING, JR. ... 149
Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis. II. Complications and Sequelae of Phreniclasis. ROGER S. MITCHELL ... 168
Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis. III. The Effect of a Paralyzed Hemidiaphragm on the Results of Homolateral Thoracoplasty. ROGER S. MITCHELL ... 183
Physical Therapy in Postthoracoplasty. One Year's Notes and Observations. JACOB GOLDBERG, RALPH FRIEDLANDER, HARRY B. DOPPELT, and DOROTHY E. MILLER ... 189
Concerning the Location of Pulmonary Infarction. EUGENE I. ZINS ... 206
Factors Affecting the *in vitro* Cytolysis of White Blood Cells by Tuberculin. CUTTING B. FAVOUR, PAUL FREMONT-SMITH, and JOSEPH M. MILLER ... 212
A Simplified Guinea Pig Test for Tuberculostatic Agents. F. I. DESSAU, R. L. YEAGER, and M. KULISH ... 223
An Evaluation of a Method of Obtaining Gastric Washings. JAMES B. HOLLOWAY, JR. and MARTIN CUMMINGS ... 228
Case Reports:
Pathological and Experimental Studies of Boeck's Sarcoid. 1. Report of a Case with Panarteritis, Periarteritis, Terminal-hypertension and Uremia, and the Reproduction of a Sarcoid-like Lesion in Guinea Pigs. SOL ROY ROSENTHAL ... 236
Erythema Induratum Bazin. Report of a Proved Case Associated with Tuberculous Lymphadenitis, Completely Relieved by Tuberculin Desensitization. THEODORE T. FOX, HENRY L. JAFFE, and LOUIS LICHTENSTEIN ... 249
Pulmonary Adenomatosis. Report of a Case. BENJAMIN FREEDMAN ... 258
Editorial: Integration of Streptomycin with other Forms of Therapy for Pulmonary Tuberculosis. JOHN B. O'CONNOR ... 264
Letters to the Editors: A Pyridine Derivative and Experimental Tuberculosis. H. J. CORPER, MAURICE L. COHN, and WM. H. FREY ... 269
Abstracts ... 17

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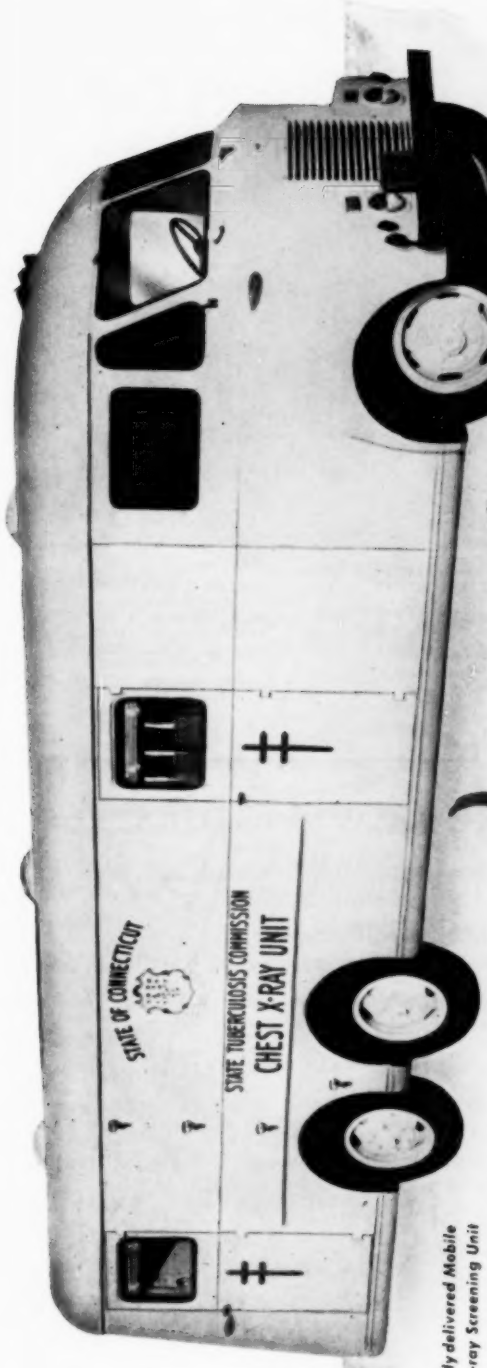

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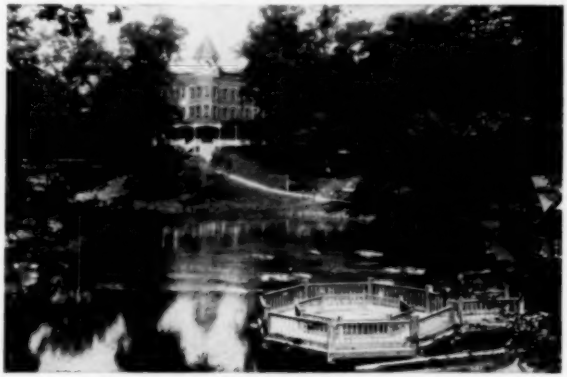

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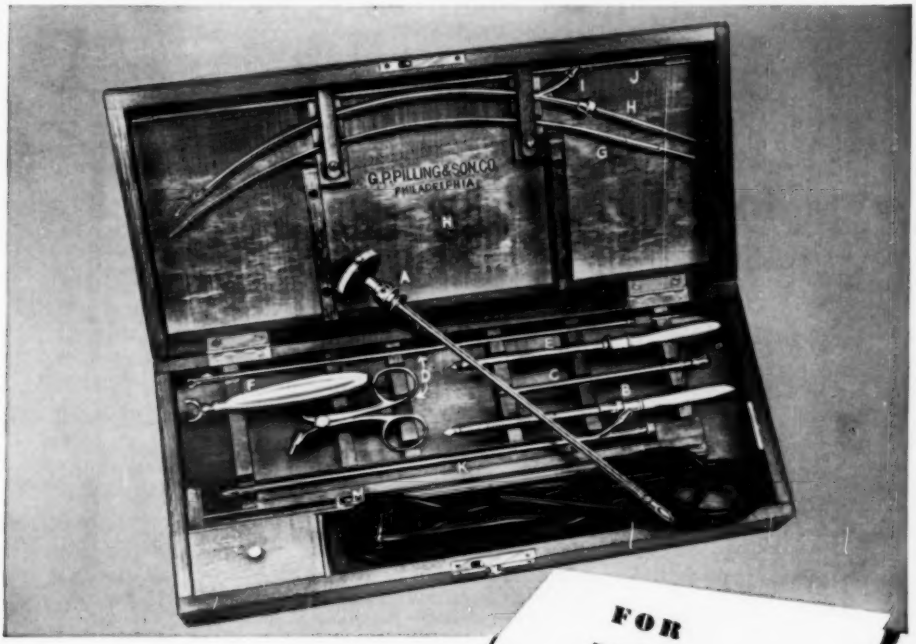

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SIMPLE TESTS OF VENTILATORY FUNCTION FOR USE IN THE SANATORIUM OR CLINIC[1, 2]

FREDERICK C. WARRING, JR.

(Received for publication March 1, 1949)

INTRODUCTION

About seven years ago a series of talks and articles on bronchospirometry (1, 2, 3, 4) aroused widespread interest in this country in the subject of pulmonary function. After an initial wave of enthusiasm, many chest physicians and thoracic surgeons abandoned thoughts of utilizing functional tests because they thought that the necessary apparatus was too complicated and expensive, detailed knowledge of pulmonary physiology was needed to execute and understand the procedures, and the performance of the tests would be too consuming of their time. Consequently, at the present time detailed respiratory studies are being carried on in a very few centers, but none are being done in a majority of institutions or by most practitioners. It is not generally appreciated that there are some simple, practical tests of pulmonary function which can give much needed information concerning many patients with lowered breathing reserve. These tests can be performed by any clinician or surgeon without expert knowledge of pulmonary physiology, and require the use of uncomplicated, inexpensive apparatus for only a few hours each month.

With suggestions and encouragement from Dr. George Wright of Trudeau, New York, a program of simple, practical tests of ventilation was initiated at Laurel Heights in 1942. In the past six years, 1,150 studies have been performed on 410 patients. It is obvious that simple tests of ventilation alone are inadequate if the objective is exhaustive study of pulmonary physiology. Nevertheless these simple tests have been of great practical value in the management of patients. They have served to detect the presence or imminence of dyspnea and to predict and follow the effect of collapse therapy with a degree of accuracy which is generally quite adequate for clinical purposes. To say the least, such tests have led to conclusions regarding function which have proved far more reliable than those derived from "clinical jugment" and study of chest roentgenograms.

The purpose of this paper is to describe the apparatus and the method used in performing these ventilatory tests, to show illustrations of their application, and to review the end results of function in a group of cases after operation.

The apparatus (figure 1) consists of a 100 liter Douglas Bag, a high velocity one-way valve, connecting hose and couplings, a noseclip, a converted gas meter, and a stopwatch. This entire equipment can be purchased for about two hundred dollars.

[1] From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

[2] Presented before the Fall Meeting of the Eastern Section of the American Trudeau Society at the Rutland State Sanatorium, Rutland, Massachusetts, on October 15, 1948.

METHOD

Four parts comprise this method of evaluation of a patient's ventilatory function:

(a) the walking ventilation;
(b) the maximum breathing capacity;
(c) the ratio $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ and its relationship to dyspnea; and
(d) careful fluoroscopy of the chest.

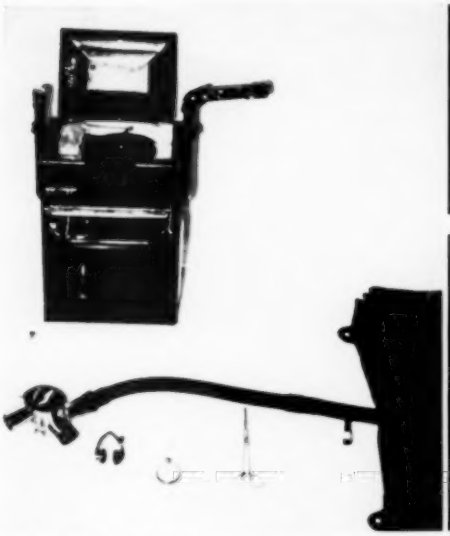


FIG. 1. (Left) The apparatus: a 100 liter Douglas Bag, high velocity one-way valve, connecting hose and couplings, noseclip, converted gas meter and stopwatch.
FIG. 2. (Right) Performing the walking ventilation test

The Walking Ventilation (*W.V.*)

The walking ventilation test is performed by having the patient walk slowly on a level surface, breathing as easily and naturally as possible through the one-way valve into the Douglas Bag. The pace is 180 feet per minute. The test is started by applying the noseclip to the patient. Then the patient merely walks for one minute beside the operator, who, during this initial period, carries both the Douglas Bag and the valve. This one minute "warm-up period" is to familiarize the patient with the pace and to bring his rate and depth of breathing to the walking level. Having done this, the patient and the operator continue to walk at the same pace, the patient is instructed to place the mouthpiece of the valve into his mouth, and the operator resets his stopwatch. As he walks for

the next three minutes, the patient breathes in a natural manner through the valve into the Douglas Bag, which is carried by the operator (figure 2). Exactly at the end of three minutes the valve is taken from the patient's mouth, the connecting hose to the bag is promptly clamped off, and the noseclip is removed. The patient is immediately questioned about the presence and degree of dyspnea. The air in the Douglas Bag is measured by running it through a gas meter calibrated in liters. The resulting figure, divided by three, gives the walking ventilation in liters per minute.

Values for the walking ventilation test vary from 7 to 30 liters per minute in different patients. Most patients have a walking ventilation in the range of 12 to 19 liters per minute. *Of importance is the fact that in the great majority of patients the walking ventilation remains remarkably constant.* For example, a patient with a walking ventilation of 14 liters per minute can be expected to have a walking ventilation at or near 14 liters per minute before and after spread of disease, before and after clearing of disease, and before and after collapse therapy.

Some other details of the walking ventilation test should be mentioned. While the test is being performed, a check on the distance covered at 15 second intervals aids in maintaining an even pace. The patient is repeatedly instructed to "breath easily, just as you do when you walk on the ward." Occasionally an apprehensive patient will give an initial artifically high value for his walking ventilation. If this is suspected, or if the patient has a walking ventilation of 20 liters or more on the first test, it should be repeated a second or third time the same day or later to determine the true level.

Degree of dyspnea at the conclusion of the walking test is recorded as:

none
slight (aware of labored breathing, but not uncomfortable)
moderate (uncomfortable, but could continue walking); or
severe (could not continue walking or did not complete the test).

Dryness of the throat should not be confused with slight dyspnea.

The Maximum Breathing Capacity (M.B.C.)

The maximum breathing capacity is determined by having the patient breath as hard and as fast as he can for exactly 30 seconds through the high velocity one-way valve into the Douglas Bag (figure 3). The air in the bag is measured by passing it through the gas meter. The resulting value, multiplied by two, gives the maximum breathing capacity in liters per minute. A healthy male has a maximum breathing capacity of about 150 liters per minute and a healthy female, a maximum breathing capacity of about 100 liters per minute. Any disease or condition which impairs the function of the pulmonary parenchyma, the pleurae, the ribs, the diaphragm, the bronchi, or any combination of these five anatomical components of the chest, proportionately reduces the maximum breathing capacity.

Careful effort is made to get the patient to put forth his best effort when doing the maximum breathing capacity. Most patients perform best in a sitting position, in a chair, or with their legs hanging over the side of the bed. It is worth-

while to have a new patient watch an experienced one do both the walking ventilation test and the maximum breathing capacity before attempting it himself. Some patients, in a spirit of competition, exert themselves more before an audience of one or two other patients who are awaiting their turn. Care must be taken that the nose clip is snug and that the patient does not remove his lips from the mouthpiece. The importance of the test to the patient is emphasized and reassurance should be given that the test will not result in spread of disease or hemoptysis. The patient is instructed to "breathe as hard and fast as you can for one-half minute." Two steady, deep breaths a second is a good rate. Rates of breathing that are too slow or too rapid are inefficient. It frequently is desirable to mark time with the patient's breathing and to hold the stop watch before

FIG. 3. Determining the maximum breathing capacity

him. The patient should be encouraged to his very best effort during the entire 30 second period. Unless both the operator and the patient are satisfied that the exertion has been maximum, the test is repeated on the same day or later. By observing these precautions, the maximum breathing capacity can be reproduced within 5 per cent.

Relationship of the Ratio $\frac{\textit{Walking Ventilation}}{\textit{Maximum Breathing Capacity}}$ *to Dyspnea*

There is a definite relationship between the ratio $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ and the presence and degree of dyspnea (5).

When $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ is below .35, dyspnea is not present.

When $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ approximates .35, slight dyspnea is present.

When $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ approximates .45, moderate dyspnea is present.

When $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ exceeds .50, severe dyspnea is present at the end of the walking test.

Two important facts must be kept in mind: first, *the walking ventilation remains constant in the individual patient;* and, second, *dyspnea upon walking becomes severe as the ratio* $\frac{\textit{walking ventilation}}{\textit{maximum breathing capacity}}$ *exceeds .50.* Thus, it becomes apparent that disease or collapse therapy that causes *reduction of a patient's maximum breathing capacity to a level lower than twice his walking ventilation results in severe dyspnea when the patient is walking.*

The following is a hypothetical example of the development of dyspnea with progressive lowering of the maximum breathing capacity in a patient whose walking ventilation is 16 liters per minute:

M.B.C.	*W.V.*	*RATIO* $\frac{W.V.}{M.B.C.}$	*DYSPNEA*
64 L.	16 L.	.25	none
46 L.	16 L.	.35	slight
36 L.	16 L.	.45	moderate
30 L.	16 L.	.53	severe

Fluoroscopy of the Chest

Once the determinations have been made of the breathing requirement for walking, the maximum breathing capacity, and the ratio between the two, the patient is carefully fluoroscoped. The operator's eyes should be well accommodated to darkness before beginning the examination. The chest is viewed upon quiet breathing and also while efforts are made at both slow and rapid maximum inspiration and expiration. The following details are observed: movements of the ribs and diaphragms; shift of the heart or mediastinum; evidence of "trapping" of air in a lobe or lung; and, in the patient with pneumothorax, the degree of collapse and motion of the collapsed lung, and the presence of fluid.

Rib motion and diaphragm motion of each hemithorax is recorded separately in percentages of normal as estimated by the operator. With practice this can be done with reasonable accuracy. By adding the percentages of rib motion and diaphragm motion on each side, it is possible to arrive at an estimate of the ratio of the ventilation carried on by each lung separately. Thus a patient estimated to have 100 per cent normal rib motion and 100 per cent normal diaphragm motion on the right side of the chest, and 25 per cent normal rib motion and 25 per cent normal diaphragm motion on the left side of the chest has a ratio of 200 (right) to 50 (left). Expressed in another way this means that the right lung is estimated to be doing 80 per cent of the total ventilation.

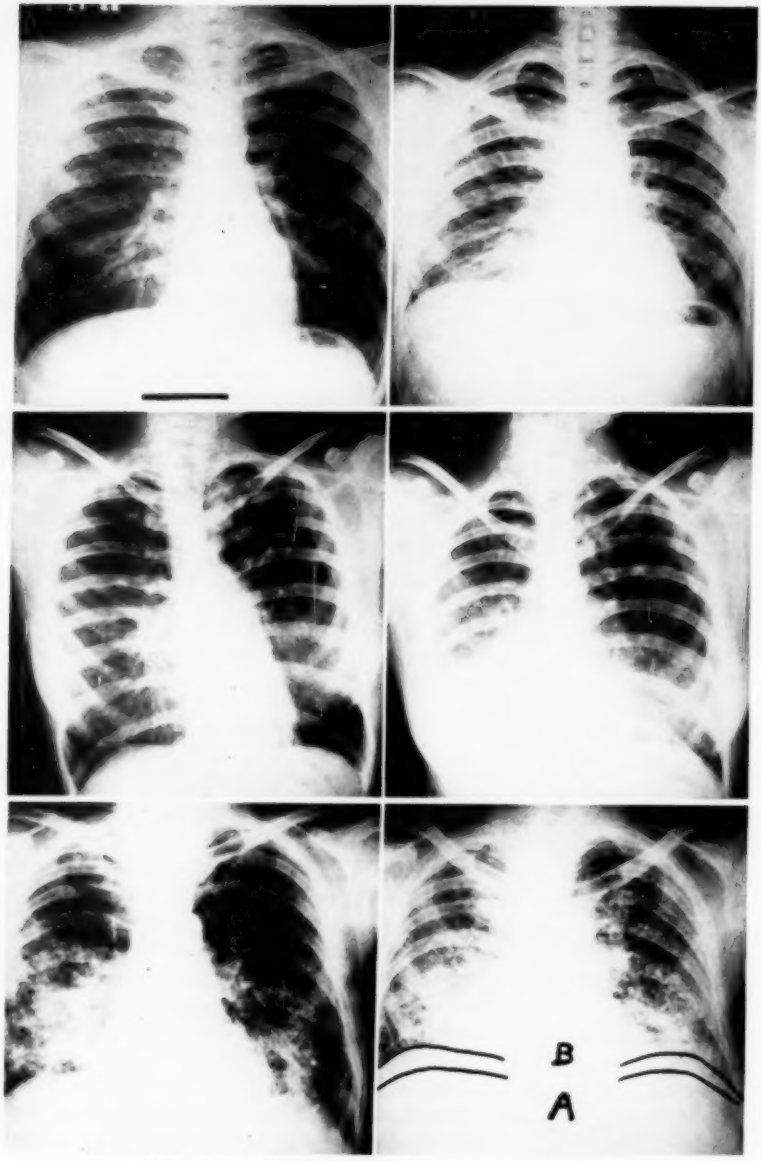


FIG. 4. (Upper left) Normal chest; deep inspiration

FIG. 5. (Upper right) Normal chest; deep expiration. There is equal "clouding" of the two lungs.

FIG. 6. (Center left) Marked stenosis of the left main bronchus; deep inspiration.

FIG. 7. (Center right) Marked stenosis of the left main bronchus; deep expiration. There is "trapping" of air in the left lung and the heart and mediastinum are pushed to the right side.

FIG. 8. (Lower left) Bilateral emphysema in a patient with silico-tuberculosis; deep inspiration.

FIG. 9. (Lower right) Bilateral emphysema. When rapid expiration is attempted the hemidiaphragms rise only part way in two seconds (A). Continued expiratory effort results in slow, progressive elevation to the maximum level (B) at the end of ten seconds.

Uniform aeration is noted throughout the lung parenchyma when the density of the normal lung at deep inspiration is observed by fluoroscopy (figure 4). When this is followed by rapid, deep expiration, emptying of the air from the parenchyma promptly produces a homogeneous haze, more dense over the lower two-thirds of the lung (figure 5). When, on attempted rapid expiration, air is retained in a lobe or lung by emphysema or by marked bronchial stenosis, the area affected fails to cloud and this phenomenon is referred to as "trapping." When trapping is a result of bronchial stenosis, the heart and mediastinum shift toward the side of the stenosis on deep inspiration and are pushed toward the contralateral side on deep expiration (figures 6, 7). If emphysema is present, the diaphragm (or diaphragms, if the condition is bilateral) may move but little at the very beginning of attempted rapid expiration and then slowly rise as the inelastic, emphysematous lung parenchyma expels the air in a period of five or more seconds (figures 8, 9). In the absence of stenosis or emphysema, deep expiration can be completed in one to two seconds.

It is important to take into consideration trapping caused by stenosis when attempting to estimate the ventilation carried on by each lung separately. If rapid breathing is being carried out, as when the maximum breathing capacity is being determined, very little air has a chance to get in and out of the lobe or lung whose bronchus is markedly stenotic. In this situation practically all of the total ventilation is performed by the other lobes the bronchi of which are patent. For example, before resection the patient with the marked stenosis of the left main bronchus (figures 6, 7) had a maximum breathing capacity of 58 liters per minute. It was estimated that nearly all of this total ventilation was being performed by the right lung and that only a small amount of air was being ventilated by the left lung distal to the stenotic bronchus. That this assumption was correct is supported by the finding of a maximum breathing capacity of 55 liters per minute after the left lung was removed at operation.

When trapping is a consequence of emphysema it must be remembered, when contemplating collapse or resection, that an emphysematous lung is a poorly functioning lung. It is often unwise, therefore, to perform thoracoplasty or resection on one lung if the contralateral lung shows signs of marked emphysema. On the other hand, performing such an operation on the emphysematous lung is possible and even may be desirable functionally if the contralateral lung is not emphysematous and demonstrates evidence of sufficient ventilatory reserve.

Conditions other than stenosis of the bronchus can produce mobility of the mediastinum. Movement of the mediastinum to a diseased side on inspiration may denote the presence of fibrosis reducing the elasticity of the parenchyma of that lung. With pneumothorax a mobile heart and mediastinum may shift to the contralateral side on expiration.

If lobes collapsed by pneumothorax expand and contract well with inspiration, it is an indication that ventilatory function is well preserved in those lobes.

Thus it may be seen that much information relative to the total ventilation and to the individual ventilation of the two lungs can be gained, with experience, from careful fluoroscopy.

APPLICATION OF VENTILATORY TESTS

Thoracoplasty

Since thoracoplasty is an irreversible procedure, it is essential to determine in advance whether or not the patient has enough breathing reserve to tolerate this operation. As a corollary to this, the surgeon wishes to know how many ribs he can remove, if necessary, or to how few ribs he must limit his collapse. *The walking ventilation remains constant before and after thoracoplasty and severe dyspnea occurs on walking when the ratio* $\frac{\textit{walking ventilation}}{\textit{maximum breathing capacity}}$ *exceeds .50. It follows then that the maximum breathing capacity in any individual patient must not be reduced by operation to a level below twice the patient's walking ventilation if severe dyspnea on walking is to be avoided.* Moreover, in our experience, in order to avoid dyspnea, it is necessary that the patient be left after operation with a maximum breathing capacity of not less than 30 liters per minute, no matter how low his walking ventilation may be.

When the maximum breathing capacity before operation is high, the reserve is ample and no concern is felt about thoracoplasty even though the thoracoplasty side is contributing a fair amount of the total ventilatory function and the operation must be an extensive one.

Example: (Case 1) The patient was a 33 year old male with a four centimeter cavity in the apex of the left lung (figure 10). His maximum breathing capacity was 136 liters before operation. Walking ventilation was 18 liters. As twice 18 is 36 liters, the maximum breathing capacity of this patient, if necessary, can be reduced by operation to 36 liters, although it is never wise to squander function. Rib motion and diaphragm motion on the right side were both estimated to be 100 per cent of normal. The left diaphragm moved 100 per cent of normal, while the rib motion on the left was slightly reduced (75 per cent of normal). From this it is seen that the right or "good" side was contributing slightly more than half of the total maximum breathing capacity of 136 liters. The surgeon was able to remove 8 ribs on the left side without fear of producing eventual dyspnea. After operation the maximum breathing capacity was 82 liters (figure 11). Walking ventilation remained relatively constant at 19 liters. Ratio of $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ postoperatively was .23. With the ratio less than .35, the patient had no dyspnea when walking.

Likewise, it is feasible to perform thoracoplasty when the preoperative maximum breathing capacity is only moderately high, or even lower, if the operation is to be done on a poorly functioning side.

Example: (Case 2) The patient was a 40 year old woman who had active parenchymal disease and an empyema pocket on the right which required a 7-rib thoracoplasty with removal of the anterior rib sections (figure 12). Her walking ventilation was 18 liters. In this instance, as in Case 1, the maximum breathing capacity could, if necessary, be reduced to 36 liters, or twice her walking ventilation. Her maximum breathing capacity before operation was 75 liters, so that she did not have the ample reserve of the man with the maximum breathing capacity of 136 liters. On the other hand, fluoroscopy revealed that the ribs and diaphragm each moved only 25 per cent of normal on the right side as compared to 100 per cent normal motion of the left ribs and 100 per cent normal motion of the left diaphragm. Adding the percentages of rib and diaphragm motion on each side gave a ratio of 50 to 200,

or 1 to 4, in favor of the left side. Hence the left side was estimated to contribute four-fifths, *i.e.*, 60 liters of the total maximum breathing capacity of 75 liters. This was borne out by the

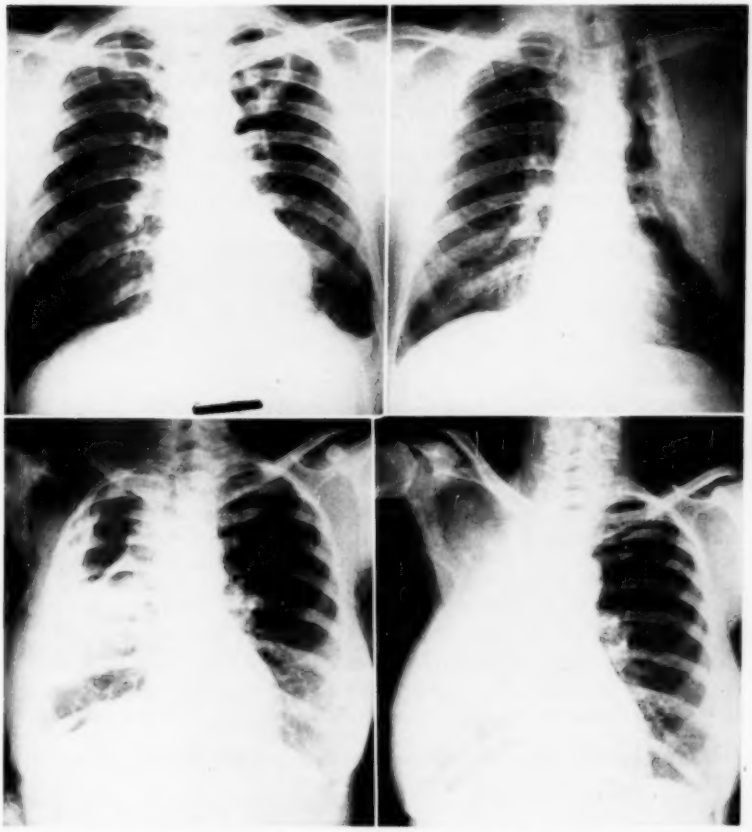


FIG. 10. (Case 1) (Upper left) Before left thoracoplasty. Rib motion: right, 100 per cent; left, 75 per cent. Diaphragm motion: right, 100 per cent, left, 100 per cent. M.B.C., 136 liters; W.V., 18 liters; ratio, .13.

FIG. 11. (Case 1) (Upper right) After left thoracoplasty. M.B.C., 82 liters; W.V., 19 liters; ratio, .23.

FIG. 12. (Case 2) (Lower left) Before right thoracoplasty. Rib motion: right, 25 per cent; left, 100 per cent. Diaphragm motion: right, 25 per cent; left, 100 per cent. M.B.C., 75 liters; W.V., 18 liters; ratio, .24.

FIG. 13. (Case 2) (Lower right) After right thoracoplasty. M.B.C., 60 liters; W.V., 19 liters; ratio, .31.

results of tests after extensive right thoracoplasty (figure 13). Elimination of the ventilation of the right lung gave a postoperative maximum breathing capacity of 60 liters. Walk-

ing ventilation remained constant at 19 liters. Ratio of $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ after operation was .31 and the patient was not dyspneic.

A patient with moderate or low maximum breathing capacity before operation may even tolerate thoracoplasty on the side of *better* function, provided the operation is sharply restricted in extent so as to produce a highly selective type of pulmonary collapse affecting only the diseased portion of the lung.

Example: (Case 3) This 36 year old woman had previously received left pneumothorax, with subsequent expansion of the left lung. Fluoroscopy revealed 75 per cent normal rib motion and 75 per cent normal diaphragm motion on the right side and only 25 per cent

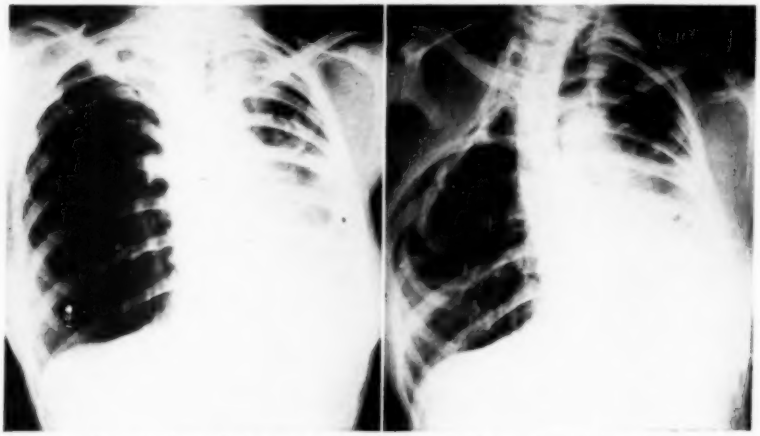


FIG. 14. (Case 3) (Left) Before right thoracoplasty. Rib motion: right, 75 per cent; left, 25 per cent. Diaphragm motion: right, 75 per cent; left, 25 per cent. M.B.C., 40 liters; W.V., 11 liters; ratio, .28.

FIG. 15. (Case 3) (Right) After selective right thoracoplasty. M.B.C., 37 liters; W.V., 13 liters; ratio, .35.

normal rib motion and 25 per cent normal diaphragm motion on the left side (figure 14). Adding the percentages of rib and diaphragm motions on each side gave a ratio of 150 to 50, or 3 to 1, in favor of the right side. She needed a thoracoplasty on the *right* for a small cavity which was fortunately situated in the extreme apex. Also in her favor was a low preoperative walking ventilation of 11 liters per minute. Her maximum breathing capacity of 40 liters per minute before operation could be reduced to our minimum standard of 30 liters. The surgeon did an excellent selective 5-rib right thoracoplasty, with partial right scapulectomy. He was careful to leave the anterior rib sections below the level of the fifth vertebral spine in order to preserve as much of the function of the lower two-thirds of the right lung as possible (figure 15). Maximum breathing capacity following operation (37 liters) was only slightly less than the preoperative value. Walking ventilation changed only to 13 liters. With the resulting ratio of $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ at .35, the patient experienced only slight dyspnea when walking on the level.

Wright has shown that the maximum breathing capacity is unchanged or actually improved in 75 per cent of patients following selective apical thoracoplasty.

Thoracoplasty can be performed while pneumothorax is maintained on the contralateral side. Serial tests of ventilatory function in such cases will give information of assistance in: (*1*) maintaining the degree of the pneumothorax at a satisfactory functional level; (*2*) deciding if thoracoplasty can be performed; and (*3*) evaluating the end results of function after thoracoplasty and subsequent expansion of the pneumothorax lung.

Example: (Case 4) The patient was a 39 year old man whose ventilatory function tests yielded the following values:

	M.B.C.	*W.V.*	Ratio $\frac{W.V.}{M.B.C.}$
February 1944—before right pneumothorax	94 L.	27 L.	.29
December 1945—with right pneumothorax	62 L.	21 L.	.34
May 1947—left thoracoplasty performed			
June 1947—after left thoracoplasty, with right pneumothorax	60 L.	23 L.	.38
June 1948—after right lung expanded	74 L.	21 L.	.28

It was essential that this man undergo a left thoracoplasty for cavitary disease. Right pneumothorax was instituted in December 1945, after fresh spread of disease on that side. Before pneumothorax the maximum breathing capacity was 94 liters. With induction and maintenance of right pneumothorax, the maximum breathing capacity was reduced to 62 liters. Seven rib left thoracoplasty was performed in May 1947, while continuing selective right pneumothorax. Maximum breathing capacity was 60 liters in June 1947, after left thoracoplasty and while the right pneumothorax was still being maintained. When the right lung was completely expanded in June 1948, the end result was a maximum breathing capacity of 74 liters. The walking ventilation initially was 27 liters. With the induction of right pneumothorax, it fell to 21 liters and remained stable at that level for the next two and one-half years while the thoracoplasty was being done and the right lung was being expanded. The patient was never dyspneic.

Ventilatory tests can demonstrate the imprudence of thoracoplasty for some patients.

Example: (Case 5) The patient was a 51 year old man with a chest roentgenogram which made it seem probable that he was a suitable candidate for left thoracoplasty. Nevertheless, ventilatory tests showed him to be a very poor risk for operation. Moreover, if thoracoplasty were to be performed, it would have to be complete because of the presence of cavities in the left apex and in the midlung (figure 16). Even though by fluoroscopy the left lung was performing only about one-seventh of the total ventilation, this patient had absolutely no reserve. His maximum breathing capacity at 35 liters was already reduced by disease to the level of twice his walking ventilation of 18 liters.

Undoubtedly complete thoracoplasty would further reduce the low maximum breathing capacity and make this patient a pitiful respiratory invalid. It must be remembered also that for a day or two following each thoracoplasty stage the maximum breathing capacity is likely to be reduced to some extent by such factors as the shock of operation, pain, and fluid in the operative site. Even though this is only a temporary slight reduction in the maximum breathing capacity, it may be just enough to precipitate an acute dangerous episode of dyspnea from which a patient without reserve may fail to recover.

It is possible to repeat the maximum breathing capacity after the individual thoracoplasty stages. Seven to thirteen days postoperatively is the best time to

do the test, for by then the patient is relatively comfortable and is able to perform satisfactorily. Thus, in a patient with a low preoperative breathing capacity the test can be repeated between stages and further operations abandoned when it is felt that the maximum breathing capacity is being reduced to an unsafe level. No one stage uniformly depresses the maximum breathing capacity more than any of the others; nor is it possible to say that a given stage will reduce the maximum breathing capacity to the same degree in every patient. These

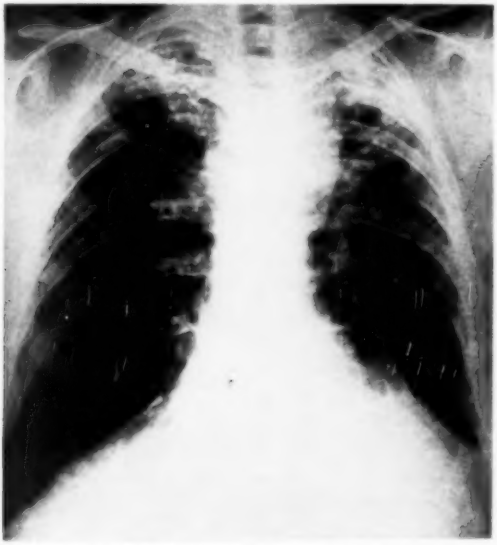


FIG. 16. (Case 5) Rejected for left thoracoplasty. Rib motion: right, 30 per cent; left, 20 per cent. Diaphragm motion: right, 100 per cent; left, 0 per cent. M.B.C., 35 liters; W.V., 18 liters; ratio, .51.

variations are related to the location and extent of the disease under collapse and to the volume of good functioning parenchyma which is being compressed.

Example: (Case 6) The patient was a 56 year old woman whose ventilatory function tests yielded the following values:

	M.B.C.	*W.V.*	Ratio *W.V./M.B.C.*
February 1944—before left thoracoplasty	71 L.	13 L.	.18
May 1944—13 days after first stage	61 L.		
June 1944—13 days after second stage	49 L.		
July 1944—20 days after third stage	38 L.		
March 1945—on one hour outside exercise	47 L.	13 L.	.28

The patient had a maximum breathing capacity of 71 liters before left thoracoplasty. This fell to 61 liters following the first stage (2 ribs), to 49 liters after the second stage (3 more ribs), and to 38 liters after the third stage (3 more ribs).

It should be observed that this patient's maximum breathing capacity increased 9 liters from the time of the last stage until the patient reached "one hour outside exercise." In our experience, a patient is unlikely to regain ventilatory function of more than 5 to 10 liters during the postoperative period as a result of exercise and improved muscle tone. Frequently the gain is less. There is good circumstantial evidence which suggests that application of tight, encircling binders to the chest for six months after thoracoplasty may cause lasting reduction of maximum breathing capacity in some cases.

Resection

Ventilatory studies are used in selecting patients for resection in much the same manner as for thoracoplasty. We have had opportunity to complete studies on 10 patients who underwent pulmonary resection. From such a small series it is not possible to draw conclusions about the need for thoracoplasty after pneumonectomy. To date our findings support the contention of those investigators who believe that many patients do not require a space-filling thoracoplasty after pneumonectomy, if protecting the function of the remaining lung is the sole objective. Thoracoplasty after resection to prevent undue strain on tuberculosis in the remaining lung is a different matter and frequently there are strong indications for this procedure.

Pneumothorax

Ventilatory studies are of use in pneumothorax patients to determine the ability of the patient to tolerate this type of treatment, to regulate the degree of collapse, and to evaluate the patient's eventual breathing capacity when the lung is expanded. Selective pneumothorax, in collapsing only diseased parenchyma, allows the good lung tissue to continue to function and in this way the maximum breathing capacity need not be reduced at all. If, however, a pneumothorax is sufficiently increased, breathing capacity is lowered in proportion to the degree of collapse of good functioning tissue.

Example: (Case 7) The patient was a 32 year old woman who had an expanded right lung from a previous pneumothorax (figure 17). On the left she had pneumothorax with 50 per cent collapse and a maximum breathing capacity of 53 liters. A cavity remained open in the left upper lobe. Walking ventilation was 20 liters. These studies revealed that the collapse could be increased, if necessary to close the cavity, until the maximum breathing capacity was reduced to two times 20, or 40 liters. This was tried, but eventually the left pneumothorax was abandoned as ineffective. Fortunately, the cavity closed as the lung expanded. During the expansion of the left lung, fluid formed in this hemithorax. Fifty-two aspirations of pleural fluid were performed before pleural symphysis was obtained (figure 18). It should be noted that the maximum breathing capacity was 104 liters after expansion in spite of the presence of pleural fluid for ten months.

Part of the present trend to condemnation of pneumothorax is based on the assumption that the persistence of pleural fluid during the course of pneumothorax, by thickening of the pleura, frequently causes severe loss of pulmonary function. At Laurel Heights it is rare that severe functional impairment sufficient to produce dyspnea accompanies or follows pneumothorax treatment.

A brief description of our general policy of management of pneumothorax cases should be stated. Pneumothorax which is obviously ineffective at the start because of gross adhesions is abandoned in one or two weeks after induction. Operable adhesions are cut within a few weeks after beginning a pneumothorax. Effective pneumothorax is maintained as "selective" as possible consistent with cavity closure and control of disease and with avoidance of an undue degree of collapse. Tuberculous empyemata and pleural effusions, persisting more than a week or two and extending to or above the dome of the diaphragm, are aspirated assiduously (6). If in the presence of fluid the pneumothorax is to be maintained tentatively, frequent aspiration with air replacement is continued until the pleural space is dry. If, on the other hand, the lung is to be expanded, aspiration

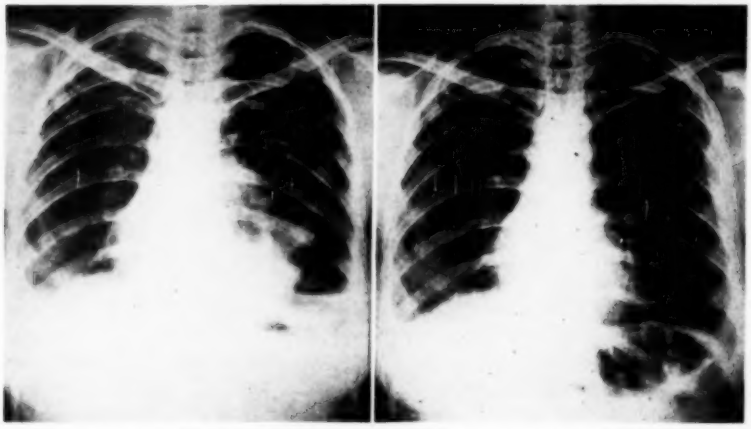


FIG. 17. (Case 7) (Left) Expanded right lung with left pneumothorax. M.B.C., 53 liters; W.V., 20 liters, ratio, .38.

FIG. 18. (Case 7) (Right) Expanded right lung. After repeated aspiration of fluid from the left chest and expansion of the left lung. M.B.C., 104 liters; W.V., 20 liters; ratio, .17.

without air replacement is continued until pleural symphysis takes place. Effective pneumothorax is maintained for two to three years after the disease is arrested.

Ventilatory studies were performed on 98 cases of pneumothorax before, during, and after expansion of the collapsed lung. All of these patients had moderately advanced or far advanced tuberculosis before pneumothorax was instituted. In 60 of these cases, there was not a sufficient accumulation of fluid to require aspiration. In 38 patients, fluid was repeatedly aspirated during the maintenance of the pneumothorax or as the lung expanded. The fact that pneumothorax treatment, even when complicated by pleural fluid, does not frequently result in severe functional impairment and dyspnea is substantiated by the ratio $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$ in these two groups after expansion of the pneu-

mothorax lung (table 1). A ratio below .35 denotes absence of dyspnea on walking. Less than 10 per cent of each group had dyspnea of any degree on walking after the collapsed lung had been expanded. This is certainly a good functional end result for any form of therapy for moderately advanced and far advanced pulmonary tuberculosis. It is believed that the end results in the cases with fluid would not be as favorable without diligent aspiration. Fluid itself, when properly managed, is not a compelling argument against the use of pneumothorax.

Phrenic Paralysis

The maximum breathing capacity was reduced more than 10 liters in 11 of 16 patients receiving temporary phrenic paralysis.

Example: (Case 9) The patient was a 53 year old man who had a maximum breathing capacity of 79 liters before operation. After right temporary phrenic paralysis, the maximum breathing capacity fell 21 liters, to 58 liters. Walking ventilation was 22 liters before operation, 21 liters after operation.

TABLE 1

Ratio of $\frac{\text{Walking Ventilation}}{\text{Maximum Breathing Capacity}}$ *and Presence of Dyspnea in 98 Patients after the Pneumothorax Lung was Expanded*

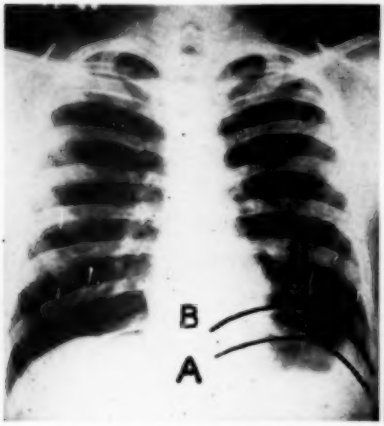
	RATIO BELOW .35, DYSPNEA NOT PRESENT	RATIO ABOVE .35, DYSPNEA WAS PRESENT
No fluid, or fluid not in sufficient amount, nor persisting sufficiently long to require repeated aspirations: 60 patients.	93 per cent	7 per cent
Fluid sufficient in amount and persisting sufficiently long to require repeated aspirations: 38 patients.	92 per cent	8 per cent

In our experience, temporary phrenic paralysis usually can be expected to lower the maximum breathing capacity 10 to 15 liters. Such a reduction is no handicap to the patient who has an initial maximum breathing capacity of 75 liters or more. When the maximum breathing capacity before phrenic operation is below 50 liters, however, such a loss of 10 to 15 liters may produce actual or imminent dyspnea.

Example: (Case 9) The patient was a 35 year old woman whose ventilatory function tests yielded the following values:

	M.B.C.
August 1946—before right phrenic paralysis	46 L.
August 1946—nerve injected with novocaine	33 L.
August 1946—5 days after crushing nerve	33 L.
October 1946—right temporary phrenic paralysis and pneumoperitoneum	28 L.
January 1947—pneumoperitoneum absorbed	32 L.
April 1947—motion returning to right hemidiaphragm	40 L.
July 1947—motion returned to right hemidiaphragm	44 L.

The patient had a maximum breathing capacity of 46 liters before phrenic paralysis. The operation was done on the right side, which, by fluoroscopy, appeared to contribute slightly more to the total ventilation than the left. After injecting the nerve with novocaine, the wound was closed and the maximum breathing capacity was redetermined and was found to be 33 liters. This was not considered too low and the wound was reopened and the nerve crushed. The reliability of this method of testing ventilation before actually crushing the nerve was demonstrated by the fact that the maximum breathing capacity was found to be 33 liters five days after the operation. Pneumoperitoneum was subsequently used to supplement the phrenic paralysis and resulted in further reduction of the maximum breathing capacity to 28 liters. At this level the patient was frequently slightly dyspneic even on strict bed rest. As this was considered undesirable, the pneumoperitoneum was soon abandoned. With absorption of the abdominal air, the maximum breathing capacity returned to 32



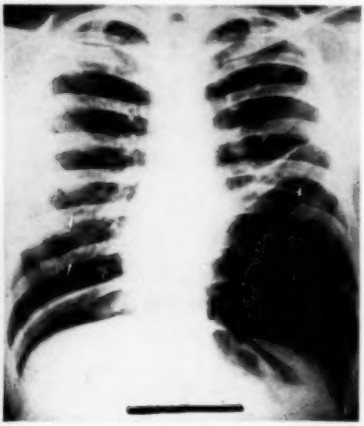


FIG. 19. (Case 10) (Left) Before left temporary phrenic paralysis. Diaphragm level at A before operation. M.B.C., 141 liters; W.V., not done

With left temporary phrenic paralysis alone. Diaphragm level at B following operation. M.B.C., 129 liters; W.V., not done.

FIG. 20. (Case 10) (Right) With left temporary phrenic paralysis supplemented by pneumoperitoneum. M.B.C., 129 liters; W.V., 26 liters; ratio, .20.

liters. As motion returned to the right hemidiaphragm, the maximum breathing capacity rose to 40 liters, and eventually to 44 liters, comparable to the pre-phrenic level.

From experience of this sort in two patients, we feel that phrenic paralysis should be done with extreme caution in patients with a maximum breathing capacity below 50 liters and especially so when the operation is to be performed on the side of better function.

Pneumoperitoneum

As employed in our sanatorium, pneumoperitoneum seldom reduced the maximum breathing capacity more than 5 liters. This was the case whether the pneumoperitoneum was used alone or as a supplement to phrenic paralysis.

Example: (Case 10) The patient was a 16 year old boy who had a left temporary phrenic paralysis which lowered his maximum breathing capacity from 141 liters to 129 liters (figure 19). Addition of pneumoperitoneum brought about no further change in the value for maximum breathing capacity (figure 20).

DISCUSSION

The method described above for the evaluation of pulmonary function relies on careful fluoroscopy for estimation of the function of the individual lungs. The criticism can be raised that accurate determination of the breathing effort of each lung is not possible without differential bronchospirometry. In fact, Wright (7), while finding satisfactory correlation of bronchospirometric and fluoroscopic data in two-thirds of his total cases, feels that serious error may occur in individual patients. On the other hand, some clinicians question the reliability of differential bronchospirometry in individual cases because of the mechanical difficulties involved in the procedure. Even the physiologists will not always quarrel with this statement.

TABLE 2

Functional End Results in 123 Patients Subjected to Operation

	MAXIMUM BREATHING CAPACITY BEFORE OPERATION		
	30 to 49 L.	50 to 69 L.	70 or more L.
Studied by ventilatory method: 123 patients.	(6 patients studied)	(47 patients studied)	(70 patients studied)
Status after operation.	1 died, 5 satisfactory	47 satisfactory	1 cripple, 69 satisfactory
Studied by differential bronchospirometry: 17 patients.	(2 patients studied)	(8 patients studied)	(7 patients studied)
Status after operation.	2 satisfactory	3 died, 5 satisfactory	7 satisfactory

In addition, the method described in the present communication utilizes only ventilatory tests and gives no information regarding oxygen intake and carbon dioxide output. These facts are of importance if the lung to be collapsed has a higher proportion of oxygen absorption in comparison to its ventilation. For example, a lung to be collapsed may be performing only 20 per cent of the total ventilation, yet may account for 40 per cent of the total oxygen absorption. This unfavorable situation does not occur often and was found only once in 26 patients who were studied preoperatively by differential bronchospirometry at Laurel Heights.

The value of a method is judged largely by the end results. One hundred and twenty-three patients, studied before thoracoplasty or resection, have come to operation and have been studied or observed postoperatively (table 2).

For analysis these patients have been divided into three groups, according to the preoperative value for maximum breathing capacity. A value of 30 to 49

liters was classified as low, 50 to 69 liters as moderate, and 70 or more liters as high. It is the 6 patients in the 30 to 49 liter group and the 47 patients in the 50 to 69 liter group who constitute the real test of the method. On the basis of the preoperative ventilatory studies, it was predicted that all of the 123 patients could tolerate operation and would not be severely dyspneic when walking after operation. In only two cases was this prediction incorrect. One patient with a preoperative maximum breathing capacity of 36 liters died from respiratory failure after operation. A second patient had a maximum breathing capacity of 75 liters before operation which was reduced by thoracoplasty to 48 liters. Unfortunately her walking ventilation was 30 liters per minute and she became a respiratory cripple, unable to walk without severe dyspnea.

An additional small group of 17 patients was studied by differential bronchospirometry preoperatively; they were considered satisfactory risks for operation. Of these, 3 in the 50 to 69 liter group had marked dyspnea, continuing to death, after thoracoplasty. Not only are the end results in the ventilatory group satisfactory in themselves, but, in our hands, they compare favorably with those of the small group which was studied by differential bronchospirometry.

In our experience, these ventilatory studies, including careful fluoroscopy, are a sufficiently accurate means for evaluation of pulmonary function in all but the exceptional case. The simplicity of the method recommends its use where the more intricate physiological tests are not available. This is not to be construed as a disparagement of the procedure of differential bronchospirometry. Nevertheless, the reality must be accepted that most physicians and clinics, because of the time, costly equipment, and expert knowledge of pulmonary physiology required, cannot or will not use bronchospirometry.

SUMMARY

Certain simple tests of ventilatory function (maximum breathing capacity, walking ventilation), combined with careful fluoroscopy of the chest, can yield much information for evaluating the presence or imminence of dyspnea in patients with pulmonary disease. In cases where collapse measures are contemplated, these ventilatory tests assist in determining the patient's ability to tolerate a given procedure.

The apparatus for performing these tests of ventilatory function and the method are described. Cases illustrating the practical application of the tests are reported and end results in 123 patients after operation are analyzed.

SUMARIO

Pruebas Sencillas de la Función Ventiladora para Empleo en el Sanatorio o la Clínica

Ciertas sencillas pruebas de la función ventiladora (máxima capacidad respiratoria, ventilación ambulante), combinadas con la cuidadosa roentgenoscopia del tórax, pueden facilitar mucha información para apreciar la presencia o la inminencia de disnea en los enfermos con afecciones pulmonares. En los casos con-

siderados para medidas de colapso, esas pruebas de la aeración ayudan a determinar la capacidad del enfermo para tolerar un procedimiento dado.

Descríbense el aparato necesario para ejecutar dichas pruebas de la función ventiladora y la técnica. Al presentar casos que demuestran la aplicación práctica del método, analízanse los resultados terminales en 123 enfermos operados.

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PHRENIC NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

II. Complications and Sequelae of Phreniclasis

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INTRODUCTION

In spite of a voluminous literature on temporary phrenic nerve interruption, there is relatively little reference to the complications and sequelae of the operation. The importance of knowledge concerning untoward effects, however, in particular the chance of prolonged or permanent loss of hemidiaphragmatic function, is well recognized (1–8).

MATERIALS AND METHODS

The material for this study was derived from two sources:

(a) 382 patients subjected to 516 phreniclases at Trudeau Sanatorium between 1932 and September 1948 (9); and

(b) 156 patients and expatients previously treated with phreniclasis by physicians[2] and at sanatoriums[3] in and around Saranac Lake, N. Y.

All of the operations in the first group and most of those in the second were performed by one of four surgeons[4]. In those performed elsewhere, some details were made available by correspondence. Chest roentgenograms were available for review by the author in 92 per cent of the first group. Follow-up data were obtained wherever necessary by correspondence with the patients, attending physicians, and with other institutions.

Ninety-six of the first group and all of the second group, 252 patients in all, were personally interviewed and fluoroscoped by the author from one to eight times between March 1947 and September 1948. Readmitted patients and expatients back for a checkup or a visit provided most of the cases followed for two years or more after operation.

In those cases first seen long after phreniclasis, the decision that hemidia-

[1] From Trudeau Sanatorium and the Edward L. Trudeau Foundation, Trudeau, New York.

[2] Doctors Daniel M. Brumfiel, John N. Hayes, Henry W. Leetch, J. Woods Price, Francis B. Trudeau, and George E. Wilson, to whom the author is indebted.

[3] New York State Hospital for Tuberculosis, Ray Brook, New York; Northwoods Sanatorium, Saranac Lake, New York; Will Rogers Memorial Hospital, Saranac Lake, New York; Veterans Administration Hospital, Sunmount, New York, to the staffs of which the author is indebted.

[4] Phreniclases by Doctors Edward S. Welles, Warriner Woodruff, Carl G. Merkel, Saranac Lake, New York; and Winfield O. Kelley, Norwich, Connecticut, to whom the author is indebted for operative data. In every instance, so far as could be determined, the technique of the operation consisted of a single crushing of the main phrenic trunk or trunks with a smooth-faced clamp 1 mm. in width, plus section of all accessories found.

phragmatic paralysis had been effected was based upon reports of serial fluoroscopic examinations in the clinical record. The examinations were made at approximately monthly intervals and consisted in a record of the excursion, measured in millimeters, of each hemidiaphragm during both quiet and deep breathing in the erect position. Moreover, the response, normal or paradoxical, of each hemidiaphragm to an inspiratory sniff was also included. According to criteria now in general use, the paralyzed side differs from the unparalyzed side as follows: (a) no descent, or a paradoxical rise, on quiet inspiration; (b) limitation of descent on full inspiration after a forced expiration; and (c) paradoxical rise on inspiratory sniff.

It was originally planned to use these criteria in the series of patients examined personally. However, largely because of additional information gained by fluoroscoping the diaphragm with the patient in the recumbent position[5], new criteria were developed and are outlined in table 3.

Diaphragmatic excursion on both quiet and deep breathing tended to be greater in the recumbent than in the erect position. This was true regardless of

TABLE 1

Range of Normal Hemidiaphragmatic Excursion in 252 Patients

POSITION	TOTAL EXCURSION IN CM.	
	Quiet breathing	Forced breathing
Erect	0.5 to 5.0	1.0 to 10.0
Recumbent	1.0 to 5.0	2.0 to 12.5

whether one hemidiaphragm was paralyzed, merely weak, or normal. Of the 252 patients fluoroscoped, 73 showed at least 1 cm. greater excursion in the recumbent than in the erect position on all examinations; 10 showed the reverse; serial observations varied in 9; and in the remainder the difference was less than 1 cm. or the observations were inconclusive. The range of normal hemidiaphragmatic excursion in these 252 patients may be seen in table 1.

True rise above the expected position of quiet expiration of a totally paralyzed hemidiaphragm was observed in 14 cases in the recumbent but not in the erect position. Frequently rise was observed in both positions, but in no instance was it present in the erect position only.

The diaphragmatic response to a short inspiratory sniff very frequently was more nearly normal, *e.g.*, prompt descent, in the recumbent than in the erect position during the period when return of function was being observed, or from five to eighteen months after phreniclasis (see table 2).

In other words, there were frequent instances where fluoroscopy in the recumbent position yielded considerable additional information. For instance, in spite of the presence of the accepted criteria for hemidiaphragmatic paralysis in the erect position, slight but definite evidence of beginning return of function

[5] Suggested to the author by Dr. George W. Wright.

was found in the recumbent position in 12 cases. This was presumably due to the freer diaphragmatic excursion seen in the recumbent position. On the other hand, 4 patients with recent phreniclasis revealed the following findings: There was some descent of the hemidiaphragm on quiet inspiration, almost normal movement on deep breathing, paradoxical response to sniff, and no "rise" in the erect position. In the recumbent position there was, in addition to the paradoxical response to sniff, no motion on quiet breathing and almost none on deep breathing, and a very definite "rise" above the level of quiet expiration. One patient in fact received an immediate repeat phreniclasis because of the absence of convincing evidence of paralysis on fluoroscopy in the erect position. The fluoroscopic observations were unchanged after the repeat operation. While again virtually fixed in the position of quiet expiration in the recumbent position, the hemidiaphragm continued to show considerable motion on both quiet and deep breathing in the erect position.

TABLE 2

Response of Previously Paralyzed Hemidiaphragms to a Sharp Inspiratory Sniff in the Erect and Recumbent Positions 5 to 18 Months after Phreniclasis

	NUMBER	PER CENT
Paradoxical in erect but not in recumbent position*	33	66.5
Paradoxical in both positions	16	33.0
Paradoxical in recumbent but not in erect position	1	0.5
Total cases	50	100.0

* In 7 of these cases there was no movement up or down in the recumbent position.

The criteria for paralysis, muscular weakness, and normal behaviour of hemidiaphragms, as finally used in the author's series, are outlined in table 3. The difference between apparent and true elevation or "rise" of the hemidiaphragm must be emphasized. Usually the recently paralyzed muscle becomes more or less fixed in the position of quiet expiration. This leads to the appearance of "rise" on the routine chest roentgenogram taken at full inspiration. In some cases, presumably due to contracting intrapulmonary diseased tissue, a paralyzed hemidiaphragm will actually rise above the level of quiet expiration, occasionally to as much as two posterior interspaces above the other side. At the other extreme it may remain fixed somewhere near the position of full inspiration, presumably because of pleural or peritoneal adhesions.

Predominance of costal breathing presented a technical problem, especially in young women. If the excursion of an ostensibly normal hemidiaphragm from full expiration to full inspiration did not traverse the normal range of about two full posterior interspaces, the examination was considered incomplete and was repeated after one week's practice in diaphragmatic breathing. Instruction in diaphragmatic breathing at the fluoroscope, however, usually made a reexamination unnecessary. Binding or holding the chest to limit costal breathing

is a method which, in the writer's experience, did not bring about full use of the diaphragm. Serial examinations made at intervals from a few days to three or four weeks showed surprisingly little variation in diaphragmatic excursion when abdominal breathing was enforced.

Another problem occasionally met was the paralysis of a hemidiaphragm in one segment with normal response elsewhere. This was probably a consequence

TABLE 3

*Suggested Criteria for Paralyzed, Weak (Atrophic), and Normal Hemidiaphragms**

FLUOROSCOPIC OBSERVATION	HEMIDIAPHRAGMATIC EXCURSION OBSERVED IN:		
	Total paralysis	Muscular weakness or atrophy	Normal
Apparent "rise": failure to descend to the position of full inspiration	Present	Present	Usually none
True elevation or "rise": upward displacement from the position of quiet expiration	Up to 2 posterior interspaces higher but frequently absent	Usually absent; occasionally present	None
Response to quiet breathing in the recumbent position	†Absent or paradoxical	Present but reduced	10 to 50 mm. and usually equal to other side
Response to forced diaphragmatic breathing in both erect and recumbent positions	Reduced 50% or more when compared to opposite side. Rarely paradoxical	Reduced	60 to 125 mm. and roughly equal to opposite side
Response to inspiratory sniff in the erect position	Paradoxical	Paradoxical, lag or normal	Normal descent
Response to inspiratory sniff in the recumbent position	† Paradoxical	Lag or normal	Normal descent

* Based upon the author's experience in the 252 cases examined fluoroscopically.
† The most significant signs of total paralysis.

of failure to interrupt a secondary phrenic nerve trunk or major accessory. Persistent total paralysis or severe dysfunction of a part of a hemidiaphragm was seen several times, occasionally years after an exairesis.

Paralysis known to have lasted three months or less was presumed to have been due to incomplete nerve crushing and was classified as an inadequate or "unsatisfactory" phreniclasis for two reasons:

1. Hemidiaphragmatic motion was usually reduced rather than abolished in these cases.

2. From a technical standpoint, a total paralysis of less than 120 days seems impossible since nerve tissue regenerates at from 0.25 to 2.5 mm. per day (10) and the distance from the point of nerve crush to the dome of the diaphragm is from 300 to 400 mm. in the adult. Using the fastest rate and shortest distance, the minimum elapsed time would therefore be 120 days.

FAILURE TO OBTAIN PARALYSIS FOLLOWING PHRENICLASIS

Incidence and Relation to the Finding and Sectioning of Accessory Phrenic Nerves

The incidence of failure to obtain hemidiaphragmatic paralysis following phrenic nerve crush has been reported in various series as follows: 0.3 per cent (11), 1.5 per cent (2), 5 per cent (6), 12.8 per cent (12).

TABLE 4

Incidence of Failure to Obtain "Satisfactory" Paralysis after Phreniclasis at Trudeau Sanatorium

1932–1947

OUTCOME	PHRENICLASIS OPERATIONS									
	First		Second		Third		Fourth		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
"Satisfactory" paralysis:										
Lasted *over* 3 months	330		95		11		1		437	
Inadequate paralysis:										
a. Lasted 3 months or less	12	9	4	14	1	27	0	—	17	11
b. No paralysis obtained	19		11		3		0	—	33	
Totals	361		110		15		1		487	

In the 487 phreniclases performed on 361 patients at Trudeau Sanatorium between 1932 and November 1947, the incidence of failure to obtain "satisfactory" paralysis, or a paralysis of over three months' duration, was 9 per cent with the first operation, 17 per cent with the second, and 27 per cent with the third (table 4).

The percentages of failure as shown in table 4 represent *50* failures to obtain "satisfactory" paralysis in *38* different patients. In 22 of these 38 patients no attempt to recrush the nerve was made for various reasons which were not always clear in the records. Of the other 16 patients on whom a second attempt to obtain paralysis after initial failure was made, 6 were successful. The incidence of failure to produce *any* successful paralysis in the series is therefore slightly less than 9 per cent. It is of interest that in each of the 6 successes after previous failure, one or more accessory nerves were sectioned on the repeat operation, when accessory nerve data were recorded.

It has been strongly emphasized (13) that a careful search for accessory phrenic nerve fibres is essential to consistent success in obtaining hemidiaphragmatic

paralysis with phreniclasis. Table 5 shows this relationship in 487 consecutive phreniclases at Trudeau Sanatorium.

At initial operation, failure to obtain satisfactory paralysis was observed in 11 per cent of those in which no accessory nerve was found, whereas failure was observed in only 5 per cent of those in which at least one accessory nerve was sectioned. At repeat operation failure was somewhat greater (14 per cent) when accessories were sectioned than when none were found (10 per cent), but the incidence of previous permanent interruption of accessories in the latter group was high.

When the operative note contained no reference to accessory nerves, the surgeon may be presumed to have been less concerned about their possible presence

TABLE 5

Relation of Success in Obtaining "Satisfactory" Hemidiaphragmatic Paralysis to the Finding and Sectioning of Accessory Phrenic Nerves

1 OR MORE ACCESSORY PHRENIC NERVES	INITIAL OPERATIONS			REPEAT OPERATIONS		
	Total	No paralysis or "inadequate" paralysis, i.e., lasted 3 months or less		Total	No paralysis or "inadequate" paralysis, i.e., lasted 3 months or less	
		Number	Per cent		Number	Per cent
Found*	143	7	5	14	2†	14
Not found	111	12	11	51	5‡	10
Complete operative data available	254	19		65	7	
No data on accessories	107	12	11	61	12	19
Total operations	361	31	9	126	19	15

* All accessories found were sectioned.

† In spite of the sectioning of accessory nerves, these two repeat operations were again failures after a previous failure.

‡ The surgical technique of repeat operations after a previous success usually did not include a careful search for accessory nerves.

and importance. The high (11 per cent) incidence of failure to obtain satisfactory paralysis in 107 such cases therefore lends further weight to the importance of a thorough search for accessory nerves at initial operations.

THE OPERATIVE COMPLICATION OF PHRENICLASIS

The following operative complications have been reported in the literature (2, 5, 11, 13, 14): injury to the thoracic duct; injury to the vagus nerve; injury to the cervical sympathetic nerves; injury to the brachial plexus; traumatic pneumothorax; and injury to the recurrent laryngeal nerve.

In the 487 phreniclases performed at Trudeau Sanatorium between 1932 and November 1947, 32 operative complications were encountered and are outlined in table 6.

Lobular atelectasis was a roentgen finding without significant accompanying

symptoms. In addition, initial and final therapeutic results observed after phreniclasis in the 16 such cases were practically identical to the results previously reported in the group as a whole (9).

The single instance of gastric dilatation complicating left-sided phreniclasis was in direct contrast to a rather high incidence previously reported (15).

One operation, not recorded as a failure, was stopped when pus welled into the wound from a suppurating tuberculous lymph node.

The incidence of all operative complications was therefore 6.5 per cent. Only 0.4 per cent of these were fatal, *i.e.*, 2 far advanced "desperate risk" cases.

TABLE 6

Complications of Phreniclasis at Trudeau Sanatorium

OPERATIVE COMPLICATIONS*	NUMBER OF CASES	PER CENT
Injury to cervical sympathetic nerve	4	0.8
Laceration of thoracic duct	2	0.4
Total technical errors	6	1.2
UNTOWARD REACTIONS TO HEMIDIAPHRAGMATIC PARALYSIS†	**NUMBER OF CASES**	**PER CENT**
Dyspnea, severe, and death same day‡	1	
death 31 days later	1	0.4
Dyspnea, moderate	7	1.4
Lobular atelectasis, severe	2	
mild to moderate	14	3.3
Severe gastro-intestinal symptoms due to gastric dilatation following left-sided operation	1	0.2
Total untoward reactions to hemidiaphragmatic paralysis	26	5.3
Total complications	31	6.5

* Five of the six operative complications occurred at repeat phreniclasis, presumably because of the difficulties of dissection through scar tissue.

† Twenty-five of the 26 untoward reactions to hemidiaphragmatic paralysis followed initial phreniclasis.

‡ Operation performed on patient in bed in a desperate attempt to stop massive recurrent hemorrhage.

None of the other complications was considered serious. In a survey of 4,697 cases (16), "serious" complications occurred in 1.2 per cent, which included 0.5 per cent deaths.

THE EFFECT OF HEMIDIAPHRAGMATIC PARALYSIS ON THE COUGH MECHANISM AS OBSERVED FLUOROSCOPICALLY

Opinion has been divided on the effect of hemidiaphragmatic paralysis on the cough mechanism. Cough and expectoration seem to be improved clinically in some cases. On the other hand, some observers believe that expectoration is made more difficult, and that there is a tendency for secretions to be retained

within the lung and bronchi. The limited data available on experimental animals (17) and on humans (18) tend to support the contention that expectoration is impaired by phrenic nerve interruption.

In the course of studying the behaviour of the paralyzed hemidiaphragm fluoroscopically, patients were asked to give a hard cough while in both the erect and recumbent positions. The behaviour of the unparalyzed hemidiaphragm on coughing was as follows: During the initial inspiration the diaphragm usually descends slightly and the glottis closes. Then as the glottis is opened, the dia-

TABLE 7

Relation of Age and Sex to Duration of Hemidiaphragmatic Paralysis after Phreniclasis

	NUMBER OF CASES	DURATION OF MONTHS		
		Mean	Median	Range
Initial phreniclases	190	7.10	6.50	3½ to 18
Sex				
Males	97	7.13	6.50	
Females	93	7.08	6.50	
	190			
Age				
15 to 25	77	6.61	6.00	
26 to 40	100	7.47	7.00	
41 to 56	13	7.80	7.00	
	190			
Repeat phreniclases	38	8.15	7.40	3½ to 18
Sex				
Males	18	8.20	7.50	
Females	20	8.10	7.30	
	38			
Age				
15 to 25	14	8.36	8.00	
26 to 40	20	8.10	7.50	
41 to 56	4	9.30	9.50	
	38			

phragm abruptly rises coincident with the expulsive effort produced by the strong contraction of abdominal and thoracic muscles. This sudden rise during the expulsive phase of cough was a very constant observation in both positions except in advanced emphysema when both leaves of the diaphragm usually descend slightly; and in the presence of pneumothorax, when the homolateral hemidiaphragm frequently remains immobile.

In the erect position the paralyzed hemidiaphragm also rises during the expulsive phase of cough, in the manner of the unparalyzed side, although occasionally this is accomplished after a slight lag, asynchronously, or in a flabby fashion.

In the recumbent position, on the other hand, the paralyzed hemidiaphragm shows a distinctly paradoxical descent during the expulsive phase of cough while the normally functioning side is rising. After the force of the cough is expended, the paralyzed half returns to its former level. This observation was made on 45 of 48 patients with total hemidiaphragmatic paralysis produced by a recent phrenic nerve crush. As function began to return, this phenomenon usually disappeared although it was observed in 14 of 132 cases during the period of muscular weakness after nerve regeneration.

THE DURATION OF HEMIDIAPHRAGMATIC PARALYSIS FOLLOWING PHRENICLASIS

Of 361 patients subjected to one or more operations of phreniclasis, there were 437 "satisfactory" paralyses (table 4). In 190 initial and 38 repeat operations, each with proved return of function based upon reports of erect fluoroscopy only, follow-up data were sufficiently complete to permit a fairly accurate determination of the duration of paralysis.

In table 7 it may be seen that the range in the duration of paralysis was three and one-half to eighteen months. This has been previously reported as from three to eighteen months (14, 19) with an average of six to nine months (19). Table 7 further shows that there is a tendency for the mean and median duration to be longer after repeat operation and a slight tendency to be longer in the older age group. There was little difference in the figures between men and women. In making this study it was further noted that if no return of hemidiaphragmatic function had been observed by about 18 months after operation, the paralysis persisted and presumbaly became permanent.

THE DEGREE OF RETURN OF HEMIDIAPHRAGMATIC FUNCTION FOLLOWING PHRENICLASIS

There are only limited data on the incidence of permanent paralysis after phreniclasis. The following figures have been previously reported: 6 to 8 per cent (16), 10 per cent (7, 8, 13), 11 per cent (6), 12.3 per cent (2), and 24 per cent when supplemented with pneumoperitoneum (20). There is even less evidence on partial permanent disability. The only specific reference found states: "In 54.8 per cent the function was moderately impaired either partly because of the lack of nerve regeneration or because of fixation of the diaphragm by adhesions" (6).

Out of 336 patients with 437 "satisfactory" paralyses (table 4), 312 were followed long and carefully enough either at the sanatorium or by the attending physicians after discharge to establish the fact that either nerve regeneration had taken place or that permanent total paralysis had resulted, on the basis of fluoroscopic examinations in the erect position.

In the process of fluoroscoping patients with previous phreniclasis, the writer gained the impression that the figures on permanent total paralysis after phreniclasis, as revealed in table 8 and in previous reports, not only were low but did not tell the whole story of persistent hemidiaphragmatic disability. In other words, quite a few hemidiaphragms revealed fluoroscopic evidence of muscular

weakness or atrophy years after disappearance of the evidence of total paralysis. As a consequence, an effort was made to fluoroscope as many subjects as possible who had had one or more successful paralyses.

In a series of 252 such individuals, the time elapsed after the most recent phrenic nerve crush varied from a few hours to over 15 years. Serial examinations

TABLE 8

Incidence of Permanent Paralysis after Phreniclasis

From the Records of all Trudeau Sanatorium Patients, 1932–1947, with Sufficient Follow-up following Phreniclasis to Permit an Accurate Determination

HEMIDIAPHRAGMATIC FUNCTION	PHRENICLASIS				
	Single		Multiple		
	Number	Per cent	Number	Per cent	
Regained:					
a) Interval known	190		38		
b) Interval unknown	44		26		
c) Total	234	96	64	93	
Permanent Paralysis: i.e., *not regained* 2 or more years after last operation	9	4	5	7	
Total	243	100	69	100	312

TABLE 9

Permanent Hemidiaphragmatic Disability Observed Fluoroscopically by the Author Two Years or More after "Satisfactory" Phreniclasis

PERMANENT HEMIDIAPHRAGMATIC DISABILITY	PHRENICLASIS				
	Total Cases	Single		Multiple	
		Number	Per cent	Number	Per cent
1. None or practically none	78	56	62	22	48
2. Slight	19	11	12	8	17
3. Moderate to severe (50% or more)	29	18	20	11	24
4. Total paralysis	10	5	6	5	11
Total cases	136	90		46	

again revealed that improvement in hemidiaphragmatic function was observed up to but seldom after 18 months after phreniclasis.

In table 9 may be seen the incidence and severity of disability observed in all 136 cases examined 2 years or more after their last paralyzing phreniclasis. The cases were derived from the entire patient and expatient population in Saranac Lake and environs. The only cases excluded were those with no or inadequate paralysis after all phreniclases performed, and those with less than a 24 months'

interval between the most recent operation and the latest fluoroscopic examinations. Any paralysis of 3 months or less duration was not considered as a successful phreniclasis for the purposes of this study. The terms "slight," "moderate," and "severe" represent rough evaluations of disability ranging from normal function on the one one hand and total paralysis on the other. "Moderate" disability was arbitrarily defined as at least 50 per cent loss of hemidiaphragmatic function, attributable as clearly as possible to muscular weakness or atrophy

TABLE 10

Relation of the Elapsed Time after Phreniclasis and the Degree of Hemidiaphragmatic Disability Observed on Fluoroscopic Examination

INTERVAL BETWEEN LAST PHRENICLASIS AND LAST FLUOROSCOPY	TOTAL NUMBER OF CASES	INCIDENCE OF 50 TO 100 PER CENT LOSS OF HEMIDIAPHRAGMATIC FUNCTION TWO YEARS OR MORE AFTER LAST PHRENICLASIS	
		Number	Per cent
24 to 35 months	51	16	31
36 to 47	26	7	27
48 months or more	59	16	27
Total	136	39	29

TABLE 11

Relation of Side of Operation and Age and Sex of Patient to Incidence of Permanent Hemidiaphragmatic Disability

FACTOR	TOTAL NUMBER OF CASES	50 TO 100 PER CENT LOSS OF HEMIDIAPHRAGMATIC FUNCTION ATTRIBUTABLE TO PHRENICLASIS AND PERSISTING FOR TWO YEARS OR MORE AFTER LAST OPERATION	
		Number	Per cent
Side of Operation:			
Left	61	22	36
Right	75	17	23
Sex:			
Male	68	21	31
Female	68	18	27
Age Group:			
14 to 35	104	26	25
36 to 56	32	13	41

only. The disabling effect of adhesions produced by pleurisy with effusion, pneumothorax with effusion, or empyema, and the limiting effect of a later thoracoplasty, were carefully considered. An appropriate part of any hemidiaphragmatic disability observed short of total paralysis ascribable to these factors was then deducted from the disability ascribed to phreniclasis.

Twenty-six per cent of patients with single phreniclases and 35 per cent with multiple phreniclases showed a persistent 50 per cent loss of hemidiaphragmatic mobility, presumably attributable to previous phreniclasis.

It is of interest that the figures for permanent total paralysis in the series examined by the author were 6 per cent with single and 11 per cent following multiple phreniclases. These figures are felt to be more nearly accurate than those derived in table 8 from sanatorium and other physicians' records, which were based on fluoroscopy in the erect position only.

In table 10 it may be seen that from a statistical standpoint there is only a very slight chance of further return of function more than two years after the last phreniclasis. The incidence of 50 to 100 per cent loss of hemidiaphragmatic function was roughtly the same in three groups of patients. In those examined in the third year it was 31 per cent. In those patients examined in the fourth year and in those examined in the fifth to fifteenth year after their last "satisfactory" phreniclasis, the incidence was 27 per cent.

It is apparent from table 11 that the incidence of permanent disability was significantly higher in the older age group and in those with left-sided phreniclasis. The patient's sex made only a slight difference.

TABLE 12

Relation of the Sectioning of Accessory Phrenic Nerves to Incidence of Permanent Hemidiaphragmatic Disability Following Phreniclasis

ACCESSORY PHRENIC NERVES FOUND AND SECTIONED	TOTAL NUMBER OF CASES	50 TO 100 PER CENT LOSS OF HEMIDIAPHRAGMATIC FUNCTION ATTRIBUTABLE TO PHRENICLASES AND PERSISTING FOR TWO YEARS OR MORE AFTER LAST OPERATION	
		Number	Per cent
One or more	48	13	27
None	25	6	24
Complete operative data on accessory nerves not available	63	20	32
Total	136	39	

In table 12 it is seen that the sectioning of accessories did not materially change the incidence of persistent hemidiaphragmatic disability in the 73 cases in which complete operative data and fluoroscopic studies two years or more after phreniclasis were both available.

COMMENT

It would appear that the paradoxical behaviour of the totally paralyzed hemidiaphragm when the patient coughs in the recumbent position should impair the ability to expectorate. By the same token, patients should be able to expectorate more readily in the erect position. It has not been possible to verify this hypothesis clinically as yet.

The explanation of this observation that the totally paralyzed hemidiaphragm responds paradoxically to cough in the recumbent and not in the erect position is not entirely clear.

If at the time of occurrence of this phenomenon the sum of thoracic and ab-

dominal pressures results in a higher supradiaphragmatic pressure in the recumbent than in the erect position, this paradoxical descent of a flaccid hemidiaphragm only in the recumbent position may be clarified. This change in relative pressures is presumed to occur for two reasons: (a) the abdominal cavity is relatively larger in the recumbent than in the erect position because of the normal upward displacement of the entire diaphragm in the recumbent position and the diaphragm is therefore less readily compressed in this position; and (b) while the postural abdominal muscles tend to relax upon change from the erect to the recumbent position, the respiratory thoracic muscles are unaffected by any change in position.

Improvement in the mobility of previously paralyzed hemidiaphragms has been observed fluoroscopically in isolated cases after as much as four years (21). This observation was not made in this series but statistically there was a slight additional gain in function in the third year after the last phreniclasis.

The most reliable evidence of hemidiaphragmatic paralysis appears to be an absence of motion on quiet breathing and/or a paradoxical response to an inspiratory sniff, when the patient is in the recumbent position. It is quite important that the sniff be a sharp, definite, inspiratory effort.

Paradoxical rise of one hemidiaphragm on inspiratory sniff with the patient in the erect position, however, has been heretofore considered the best test for paralysis. This finding indicates only weakness of the hemidiaphragm, in the writer's experience. Four patients, for instance, who had never had a phrenic nerve interruption, had paradoxical movement of one leaf of the hemidiaphragm when they were in the erect position. In addition, a paradoxical response to the sniff test in the erect position may persist for months after nerve regeneration has definitely occurred, as evidenced by clear-cut descent of the diaphragm on quiet inspiration, especially with the patient in the recumbent position. On the other hand, no descent of the hemidiaphragm on quiet breathing was observed in either position if a paradoxical response to the sniff test occurred when the patient was in the recumbent position.

SUMMARY AND CONCLUSIONS

1. The incidence of permanent total paralysis was 6 per cent after single and 11 per cent after multiple "satisfactorily" paralyzing phreniclases. Permanent loss of roughly one-half or more of hemidiaphragmatic function, attributable to phreniclasis, was 26 per cent after single and 35 per cent after multiple operations. This incidence was significantly higher in patients past 35 and in left-sided operations.

2. The incidence of failure to obtain "satisfactory" hemidiaphragmatic paralysis with phreniclasis was 9 per cent for the first operation, 14 per cent for the second, and 27 per cent for the third.

3. Success in obtaining "satisfactory" paralysis was found to be directly related to the finding and sectioning of accessory phrenic nerves.

4. The behavior of the paralyzed hemidiaphragm during the expulsive phase of cough was found to differ in the erect and recumbent positions.

5. The duration of temporary hemidiaphragmatic paralysis following phreniclasis was found to vary from three and one-half to eighteen months, with a mean and median duration between six and one-half and nine and one-half months.

6. The 6.5 per cent operative complications of phreniclasis and untoward reactions to hemidiaphragmatic paralysis were minor, except in two fatal cases (0.4 per cent), only one of which may be considered a direct complication of phreniclasis.

SUMARIO Y CONCLUSIONES

La Interrupción del Frénico en el Tratamiento de la Tuberculosis Pulmonar.

II. Complicaciones y Secuelas de la Freniclasia

1. La incidencia de parálisis total permanente llegó a 6 por ciento cuando las freniclasias "satisfactoriamente" paralizantes fueron únicas y a 11 por ciento cuando fueron múltiples. La pérdida permanente de aproximadamente la mitad o más de la función hemidiafragmática, imputable a la freniclasia, representó 26 por ciento después de las primeras y 35 por ciento después de las segundas, siendo la incidencia significativamente mayor en los enfermos de más de 35 años y en las operaciones en el lado izquierdo.

2. La incidencia de fracasos en la obtención de parálisis hemidiafragmática "satisfactoria" fué de 9 por ciento para la primera operación, 14 por ciento para la segunda y 27 por ciento para la tercera.

3. El éxito en la obtención de parálisis "satisfactoria" resultó hallarse directamente enlazado con la localización y resección de los nervios frénicos accesorios.

4. La duración de la parálisis hemodiafragmática temporal consecutiva a la freniclasia varió de tres meses y medio a dieciocho meses, con una duración media y mediana de seis meses y medio a nueve meses y medio.

5. El 6.5 por ciento de complicaciones operatorias de la freniclasia y de reacciones adversas a la parálisis hemidiafragmática fueron de importancia secundaria, excepto en dos casos letales (0.4 por ciento), sólo uno de los cuales puede considerarse como complicación directa de la freniclasia.

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PHRENIC NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

III. The Effect of a Paralyzed Hemidiaphragm on the Results of Homolateral Thoracoplasty

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INTRODUCTION

A recent survey has shown that after a single paralyzing phreniclasis, while there is only a 6 to 10 per cent chance of total permanent paralysis, there is a 26 per cent chance of permanent loss of at least half the function of the hemidiaphragm (1). The chance of this partial diability was further found to rise to 35 per cent when a second phreniclasis was successful in paralyzing the hemidiaphragm, and to 41 per cent in all patients past 35 years of age.

The fact that thoracoplasty may be later indicated in patients presenting indications for phreniclasis is well known. For instance, by the end of 1947 subsequent homolateral thoracoplasty had been performed in 15 per cent of all patients treated with phreniclasis at Trudeau Sanatorium from 1932 through 1944. Although a paralyzed hemidiaphragm has been considered a contraindication to homolateral thoracoplasty by several observers (2 to 8) details on actual experience in this situation have not been found in the literature.

MATERIALS AND METHODS

The material for this study consisted of 103 patients of Trudeau Sanatorium treated with thoracoplasty before December 31, 1944. All Trudeau Sanatorium patients treated with thoracoplasty after a preceding phrenic nerve interruption provided 55 of these cases[2]: the other 48 consisted of all other patients treated with thoracoplasty at Trudeau Sanatorium from the first case in 1927.

The preoperative, operative, postoperative, and follow-up data in these cases were derived from the Sanatorium records and from correspondence with various attending physicians, surgeons, other institutions, and the patients themselves.

These 103 thoracoplasty cases were divided into two main groups, according to the functional status of the diaphragm at the time of the first stage of thoracoplasty.

Normal diaphragm at the time of thoracoplasty: Sixty-two patients had normal diaphragmatic function at the time of thoracoplasty. In 48 of these, the phrenic nerve had never been interrupted; in the other 14, there was satisfactory fluoroscopic evidence of return of hemidiaphragmatic function after a previous phrenic nerve interruption.

[1] From Trudeau Sanatorium and the Edward L. Trudeau Foundation, Trudeau, New York.

[2] Twenty-eight of these patients had thoracoplasty performed subsequent to their discharge from Trudeau Sanatorium.

Partial or total homolateral hemidiaphragmatic paralysis at the time of first stage thoracoplasty: Forty-one patients had some degree of impairment of hemidiaphragmatic function at the time of thoracoplasty. In 27, the paralysis was total, including 13 exaireses[3]; in the other 14, fluoroscopy revealed at least partial disability before the first stage. The fluoroscopic data on these 14 cases unfortunately were insufficient to permit a clear distinction between paralysis and muscular

TABLE 1

Comparability of Two Series of Thoracoplasties Performed with and without a Disabled Homolateral Hemidiaphragm

	PARTIAL OR TOTAL PARALYSIS AT TIME OF FIRST STAGE THORACOPLASTY			NO PRIOR PHRENIC NERVE INTERRUPTION OR HEMIDIAPHRAGMATIC FUNCTION HAD BEEN REGAINED BEFORE FIRST STAGE THORACOPLASTY
	Became Permanent*	Temporary or Presumably Temporary†	Total	
Total Cases: 103	19	22	41	62
Preoperative Data				
Age:				
Range	26 to 50	24 to 50	24 to 50	20 to 63
Mean and Median	33	33	33	33
Sex:				
Males	58 %	48 %	54 %	40 %
Extent: Far Advanced	58 %	48 %	54 %	44 %
Endobronchial tuberculosis found on bronchoscopy (48 different patients examined)	36 %	35 %	36 %	33 %
Operative Data				
Average number of stages	2.4	2.6	2.5	2.5
Average number of ribs resected	7.7	7.7	7.7	7.5
Year of operations:				
Range	1928–1944	1935–1944	1928–1944	1932–1944
Mean and median	1935	1939	1937	1939
Postoperative Data				
Years of follow-up of living patients:				
Mean	9.6	7.7	8.4	7.3
Median	8.2	7.5	7.8	7.0

* 13 intentional due to exairesis and 6 unintentional following phreniclasis.

† Phreniclasis with function ultimately regained in 18; no postthoracoplasty fluoroscopic studies available in 4.

weakness. These 41 cases were further subdivided into: *postthoracoplasty return of hemidiaphragmatic function* (22 cases) and *permanent homolateral paralysis* (19 cases).

These two series of cases were then examined with regard to various factors which might interfere with the accuracy of a statistical comparison (table 1).

[3] All performed before 1934.

It was found that the essential differences between the two main groups were that in those with a paralyzed hemidiaphragm before surgery there was a higher prevalence of far advanced disease, and that the thoracoplasties were performed in earlier years chronologically.

The subdivision with disability ultimately determined to be permanent included 13 exaireses and hence contained a preponderance of the earlier thoracoplasties, since the last exairesis in this series was performed in 1934. Exclusion of these 19 cases left 22 cases which, with regard to the attributes considered in table 1, were comparable to the series of 62 patients with a normally functioning diaphragm at the time of thoracoplasty.

RESULTS

In table 2 may be seen the incidence of immediate postoperative roentgenographic spread of disease and of generalized cloudiness throughout the lung under collapse interpreted as "atelectasis" or airlessness plus congestion. The latter

TABLE 2

Incidence of Immediate Postoperative Thoracoplasty Complications in 103 Patients with and without a Disabled Homolateral Hemidiaphragm

	PARTIAL OR TOTAL PARALYSIS	NO PARALYSIS
Total Cases: 103	41	62
Spread of disease after one or more stages:		
Homolateral	2	1
Contralateral	4	6
Bilateral	3	6
Total	9 (22%)	13 (21%)
Homolateral "atelectasis" after one or more stages	4 (10%)	1 (1.6%)

complication was diagnosed only when there was an associated shift of the mediastinum toward the cloudyside. Intrapleural and extrapleural effusions, which may also cause general cloudiness, were excluded on the basis of the position of the heart and mediastinal structures.

It will be noted that there was little difference in the incidence of postoperative spread of disease in the two series.

The incidence of homolateral atelectasis, however, was 10 per cent in the group with a disabled homolateral hemidiaphragm at the time of surgery, whereas it was only 1.6 per cent in the group with a normally functioning diaphragm. Unfortunately, preoperative bronchoscopy had not been performed on any of the patients in whom this complication was diagnosed.

In table 3 may be seen the details of late therapeutic results after thoracoplasty in the same series of patients. Results were classified as "satisfactory" and "poor." "Satisfactory" was applied to those cases which recovered after thoracoplasty, either promptly (within one year) or slowly (within two years)

and then remained well and working, cavities closed[4] and sputum negative for *M. tuberculosis*[5] for three years after the last stage.[6]

"Poor" results were defined as: (*1*) immediate operative deaths; (*2*) deaths from progressive tuberculosis within three years; (*3*) lapse into a state of chronic tuberculosis with "positive sputum" and/or persistent cavitation and/or severe respiratory embarrassment; (*4*) initial success, but with a significant relapse in one or both lungs within three years after the last thoracoplasty stage. One patient who died of a cause other than tuberculosis and 4, in whom postthoracoplasty follow-up data of at least three years' duration were not available, were excluded from statistical analysis but were included in computing the margin of error.

The incidence of "satisfactory" results in the patients with a normal homolateral hemidiaphragm was 73 ± 2 per cent, while in the entire group with a disabled homolateral hemidiaphragm it was 56 ± 1 per cent.

It was further observed that approximately the same percentage of "satisfactory" results was obtained in the group with permanent paralysis (58 ± 0 per cent) as in the group with temporary or presumably temporary paralysis (55 ± 5 per cent).

DISCUSSION

While immediate postthoracoplasty spread of disease was apparently unrelated, there was a definite tendency for both postoperative atelectasis and poor late results to occur in patients with preoperative evidence of a disabled homolateral hemidiaphragm.

It is not certain how much of this difference in late results after thoracoplasty may be attributed to the condition of the diaphragm at the time of operation, since so many variables enter into the picture. On the other hand, the difference in the two series is felt to be significant in spite of the limited number of cases. It should be pointed out, however, that the group with permanent paralysis is not wholly comparable to the other two groups because the mean year in which thoracoplasties were performed was three years earlier.

From a theoretical standpoint it is actually surprising that atelectasis did not occur more frequently in the presence of hemidiaphragmatic paralysis. During the period of decostalization and pain following a thoracoplasty stage, the burden of partial or total abolition of the costal component of breathing is thereby added to a lung, the ventilatory function of which is already impaired by partial or total hemidiaphragmatic paralysis. Pooling of secretions is probably also promoted in this situation by the paradoxical behavior of the paralyzed hemidiaphragm during cough when the patient is in the recumbent position (1). Most patients with recent thoracoplasty necessarily spend considerable time in this position. Any impairment of the mechanism of drainage of bacilli-laden secretions might be expected to increase the incidence of postoperative spread of

[4] On stereoscopic or flat chest roentgenograms.

[5] Three or more negative 50 hour concentrated smears in most cases.

[6] See first footnote, table 3.

disease. While observations in the immediate postoperative period (table 2) failed to confirm this hypothesis, the group with normal diaphragmatic function seemed to handle "spreads" somewhat better, at least from the standpoint of late results (table 3).

Another theoretical objection to thoracoplasty in the absence of homolateral hemidiaphragmatic ventilatory function is the possible creation of a shunt, with the pulmonary vessels circulating blood through lung tissue which can no longer

TABLE 3

Relation of Late Results after Thoracoplasty to the Preoperative Condition of the Homolateral Hemidiaphragm in 103 Cases, 1929–1944

	PARTIAL OR TOTAL PARALYSIS			NO PARALYSIS
	Became Permanent	Temporary or Presumably Temporary	Total	
Total Cases: 103	19	22	41	62
Satisfactory				
Prompt recovery	10	10	20	35
Delayed recovery	1	1	2	8
Total	11 (58 ± 0%)	11 (55 ± 5%)	22 (56 ± 1%)	43 (73 ± 2%)
Poor				
Operative deaths	2	1	3	4
Death from progressive tuberculosis 6 months to 3 years later	2	4	6	2
Became chronic invalid	3	3	6	7
Recovery, with significant relapse within 3 years*	1	1	2	3
Total	8 (42%)	9 (45%)	17 (44%)	16 (27%)
Nonevaluated Cases:				
Nontuberculous deaths: 1	0	0	0	1
Contact lost†: 4	0	2	2	2

* In addition to these 5 relapses occurring within the first three years, only 6 late relapses occurred among the 65 satisfactory results in the ensuing 2 to 16 years of additional postthoracoplasty follow-up. Seven of the 11 patients who relapsed have again become arrested.

† All other cases were followed to 1947 or death.

be properly ventilated after the added ventilatory impairment of resection of segments of five or six ribs. Unsaturated arterial blood has actually been obtained under such circumstances in a few instances (9, 10).

SUMMARY AND CONCLUSIONS

1. Late results with thoracoplasty in a series of 103 patients were less favorable when the homolateral hemidiaphragm was partially or totally disabled at the time of operation.

2. The frequency of spread of disease after thoracoplasty stages was not altered by disability of the homolateral hemidiaphragm at the time of operation.

3. The incidence of general atelectasis of the homolateral lung after one thoracoplasty stage was 10 per cent in patients with a simultaneously disabled homolateral hemidiaphragm and 1.2 per cent in patients with a normal diaphragm.

SUMARIO Y CONCLUSIONES

La Interrupción del Frénico en el Tratamiento de la Tuberculosis Pulmonar. III. Efecto de una Parálisis Hemidiafragmática sobre el Resultado de la Toracoplastia Homolateral

1. Los resultados tardíos de la toracoplastia en una serie de 103 enfermos fueron menos favorables cuando el hemidiafragma homolateral se hallaba parcial o totalmente incapacitado en el momento de la operación.

2. La incapacitación del hemidiafragma homolateral no alteró la frecuencia de la difusión de la enfermedad después de los distintos tiempos de la toracoplastia.

3. La incidencia de atelectasia general del pulmón homolateral después de un tiempo de la toracoplastia representó 10 por ciento en los enfermos con un hemidiafragma homolateral incapacitado simultáneamente y 1.2 por ciento en los que tenían diafragmas normales.

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PHYSICAL THERAPY IN POSTTHORACOPLASTY[1, 2]

One Year's Notes and Observations

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GENERAL CONSIDERATIONS

The relatively recent employment of physical therapy in postthoracoplasty work has prompted us to keep careful records and to recount our notes and observations in this report, in order to supplement in detail the excellent articles (5, 6, 7, 10) already published on the subject.

The work was carried out in a 619 bed Veterans Administration hospital for tuberculous patients.

The purpose of the study was to observe the skeletal and the muscular function changes which result from the thoracoplasty operations and to determine whether these changes can be prevented or minimized to any extent. Towards these ends the patients' chest roentgenograms were studied to note spinal deviations. In addition, photographs were taken preoperatively, between stages, and postoperatively, and postural examinations were made along with the photographs. Muscle function tests were done in a limited way during the physical therapy program in order to compare the muscle function on the operated side with that on the nonoperated side. More complete information about muscle function was gained from those thoracoplasty patients who were on the ambulant ward and whose work tolerance permitted more detailed examination.

During the year October 1946 to October 1947, 60 patients were seen. Of this number 21 patients had already undergone surgery when the present program of physical therapy was started in October 1946. These 21 patients ranged from one who had the first surgical stage fourteen months previously to those who were still undergoing further surgery. Included in the total were 7 patients who had surgery at other Veterans Administration hospitals and who came to this hospital for convalescent care. While we are not entirely familiar with the physical therapy given those who were not under our care from the start, the photographs taken and the chest roentgenograms of these patients studied did help us to find out, without considering their previous physical therapy, what changes may result from thoracoplastic operations.

The patients were all males ranging in age at the time of surgery from 21 to 53, with an average age of 33. Slightly more than 50 per cent were in the 20 to 29 age group.

[1] From the Physical Medicine Rehabilitation Service, Veterans Administration Hospital, Castle Point, New York.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

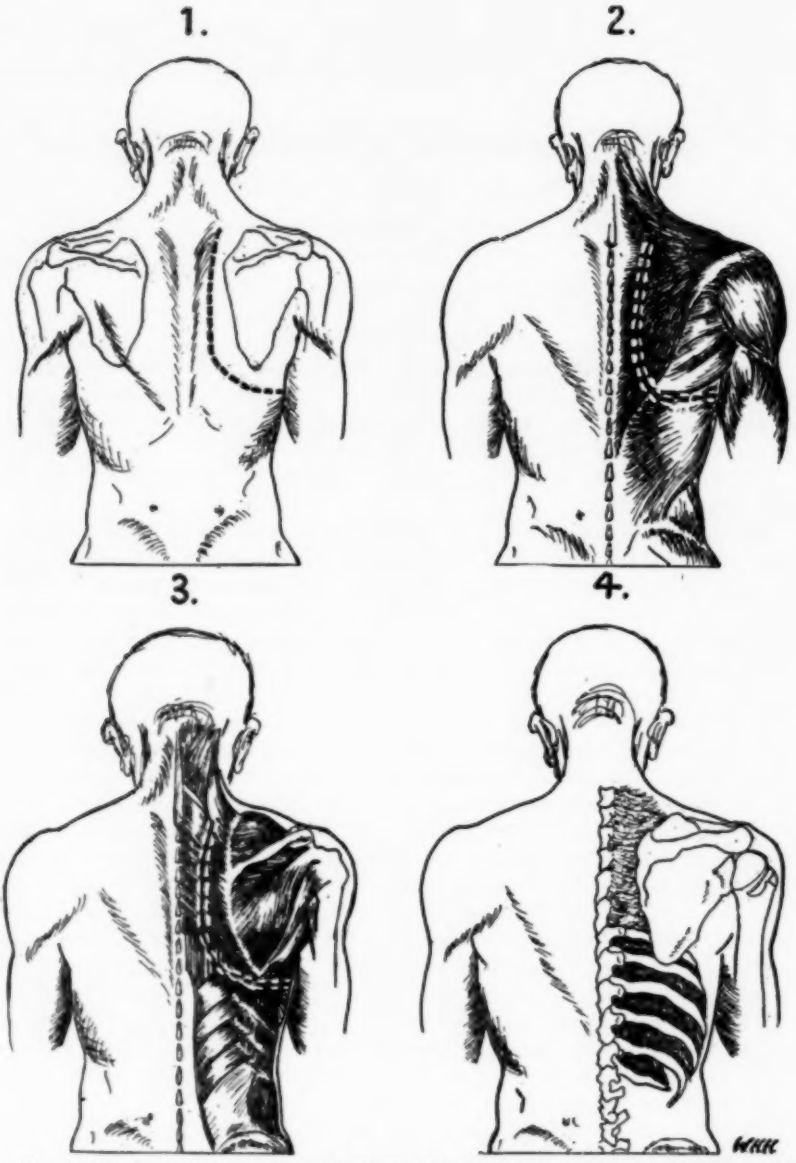

FIG. 1. The skin incision starts at the base of the neck between the spinal column and the scapula, proceeds downward and curves under the inferior angle of the scapula at about the level of the eighth rib, and terminates at the mid-axillary line.

FIG. 2. The incision through the first layer of muscles cuts through the trapezius and the latissimus dorsi.

FIG. 3. Through the second layer of muscles the incision traverses the rhomboideuxs minor and major and the lower digitations of the serratus anterior near its insertion.

FIG. 4. Shows the defect resulting from the removal of several ribs including the transverse processes to which they are attached. The overlying and adjacent structures have been omitted for convenience of illustration. Actually the periosteum and its muscular attachments remain on the chest wall. The erector spinae muscles are retracted medially during the operation and portions of this muscle group are separated from the parts resected.

Photographs, notes, and observations made on the original 60 patients subsequent to October 1947 and up to the final draft of this article will be included.

THE THORACOPLASTY PROCEDURE

A brief description of a thoracoplasty operation follows to acquaint the readers with the structures involved and the postoperative physical therapy problems encountered.

A thoracoplasty consists of a subperiosteal resection of ribs for the purposes of permanently collapsing the chest wall in order to relax the lung or to obliterate an empyema space. Surgery is performed in one to four stages, depending on the site of the cavity. If the cavity in the lung is in the apex, only one or two stages may be necessary. Lesions situated lower in the lung may require up to four stages and the resection of ten ribs. The usual surgical procedure at this hospital involved a seven rib resection done in three stages. The first three ribs are resected during the first stage. Ribs 4 and 5 are removed during the second stage, and the next two ribs are taken at the third stage. Multiple stages, or operations, are done to lessen the effects of surgical shock and paradoxical respiration, and thereby to reduce the operative risk.

It should be noted that nothing is done to the affected lung itself. By removing the supporting rib structure the chest wall collapses and the underlying lung is permitted to relax and conform to the newly contoured chest wall. Compression by the shoulder girdle and scapula also plays a part in delineating the new contour of the chest wall.

The thoracoplasty procedure (figures 1, 2, 3, 4) consists essentially of an incision starting at the base of the neck, between the spinal column and the vertebral border of the scapula, and proceeds downward between these structures, curving outwardly under the inferior angle of the scapula and terminating at the mid-axillary line (figure 1). The first layer of muscles incised are the trapezius and the latissimus dorsi (figure 2). The second muscular layer consists of the rhomboideus minor and major and the digitations of the serratus anterior (figure 3). Then the vertebral border of the scapula is lifted and the origins of the serratus anterior muscle are separated from the upper five or six ribs. This permits the scapula to be retracted laterally. The erector spinae muscles are retracted medially and a subperiosteal rib resection is done, including the transverse processes. The periosteum and the muscles separated from the resected structures remain on the chest wall. Bone regeneration starts from the periosteum, forming a firm, newly-contoured chest wall and maintaining the lung in a permanently collapsed position. The entire process of rib regeneration requires about four months.

Figure 4 shows a chest from which several ribs and vertebral transverse processes have been removed. The muscular structures have been omitted for convenience of illustration. The muscles which are separated from the resected skeletal structures soon reattach themselves to the adjacent tissues.

Some of the affected muscles about whose functions we are concerned are the trapezius, latissimus dorsi, rhomboidei, serratus anterior, pectoralis major, erector spinae, and the scaleni group.

The stages of surgery are usually performed two to three weeks apart, gaining entrance into the operative field by excision of the previous incision scar. It should be noted here that the same muscle layers are incised at each stage.

PHYSICAL THERAPY

The physical therapy program as given here represents a compromise between rest and exercise. Most of the patients undergoing a thoracoplasty have active symptoms of tuberculosis and for them the desired regimen is rest. There are some undesirable postoperative sequelae, however, such as skeletal deviations

and muscular and joint dysfunction of the shoulder girdle on the operated side. The physical therapy program entails the minimum specifically localized activity which will accomplish the desired results. These are an active full range of shoulder girdle movements, maintenance of muscle tone in the surgical area, and the preservation of a symmetrical bodily alignment.

Linduff (7) recently described the physical therapy procedures for chest surgery conditions, among them thoracoplasty. Our methods follow closely those of Linduff, being somewhat modified to meet the requirements of the staff surgeons. Whenever a question has arisen as to any particular activity being too strenuous, the choice has always been in favor of less activity.

Briefly, the following is an outline of the physical procedures used in post-thoracoplasty:

Preoperative:

1. A preoperative photograph, posterior view, is taken as a basis for comparison with the postoperative photo.
2. The patient is made acquainted with the postoperative problems:
   (a) pain and soreness of the affected muscles, interfering temporarily with the shoulder girdle movements
   (b) the possible skeletal deviations which may result from surgery are mentioned and the patient is told how to guard against them
3. The patient is shown the specific local exercises he will do postoperatively and he performs them as demonstrated by the physical therapist:
   (a) glenohumeral and shoulder girdle movements
   (b) diaphragmatic breathing
   (c) mild abdominal exercise consisting mostly of pelvic tilting for postural correction.
4. Correct bodily alignment in bed is stressed:
   (a) head and neck straight, especially after the first stage of surgery when the head and neck tend to deviate laterally towards the nonoperated side
   (b) shoulders level, the tendency being for the shoulder girdle to elevate on the operated side
   (c) the main body masses, head, thorax, and pelvis should be maintained in a straight line.

Postoperative:

1. The body alignment is checked in bed as soon as the patient is free from the effects of the anesthetic. Caution is exercised so as not to interfere with nursing care.
2. Diaphragmatic breathing is started early to encourage relaxed breathing. Chest expansion is avoided so as to facilitate pulmonary collapse.
3. Active assistive exercises are given consisting of:
   (a) the normal glenohumeral movements
   (b) horizontal abduction and adduction of the humerus
   (c) abduction and adduction of the scapula
   (d) depression of the shoulder girdle
   (e) combined movements of adduction of the scapula and hyperextension of the humerus.

The movements of adduction of the scapula, alone and combined with hyperextension of the humerus, are done in the prone-lying position when the patient is able to turn over. All other movements are carried out in the supine-lying position.

Procedure:

The exercises are usually started, with the staff surgeon's approval, on the third postoperative day. The patient is first made comfortable in the supine-lying position by placing a pillow under the knees and, if necessary, one under the head. Each movement is performed by the patient as far as he is able and then is assisted to the point within the tolerance of pain. Each movement is done twice at first. Linduff (7) suggests that at the end of the seventh day each exercise may be performed five times, twice a day. Since the emphasis at our institution is on minimum activity, the maximum for each exercise is three times, once a day. It is most essential that all movements be done slowly with adequate rest periods intervening.

Precautions:

1. A temperature of 100°F. or over contraindicates treatment.
2. If the pulse rate does not return to the pre-exercise level within five minutes after exercise, the amount of activity given the next day is reduced. Usually, even when the pulse is rather high to start with, if the exercises are given slowly with adequate rest periods between movements, the pulse will remain fairly stable. An unusually rapid pulse for a given patient contraindicates treatment.
3. Hemoptysis is a definite contraindication for treatment.
4. Other limiting factors to the exercise routine are cardiac disturbances in the older patients, or a spread of the disease in the same or into the contralateral lung, and such other indications as the thoracic surgeon in charge of the case may deem significant.

POSTTHORACOPLASTY CHANGES

The possible postthoracoplasty changes may be divided into two categories: scoliosis with its concomitant skeletal changes; and skeletal deviations of the shoulder girdle and changes in muscle function as related to the surgical trauma.

Scoliosis and Concomitant Skeletal Changes

Scoliosis, in general, may be caused by any one of several conditions, among them thoracoplasty. Regardless of the cause, the mechanism for the development of scoliosis is the same. We shall consider first the general characteristics of scoliosis and then relate these characteristics to postthoracoplasty findings.

Lovett (8) described the movements of the spinal column as four in number: flexion, extension, lateral flexion, and rotation. Considering only the dorsal and lumbar segments for the moment, flexion and extension of the spine are essentially movements of the lower two dorsal and the lumbar vertebrae. Lateral flexion is also most free in this area. Rotation is primarily a movement of the dorsal spine. Actually, lateral flexion and rotation are two elements of a compound movement; one usually accompanies the other.

Lovett (8) explains the reason for the two movements, lateral flexion and rotation, acting together on the basis of the mechanical law that governs flexible rods. When an attempt is made to bend a flexible rod in two planes at the same time, a twisting or rotation of the rod will result. In the case of the spinal column,

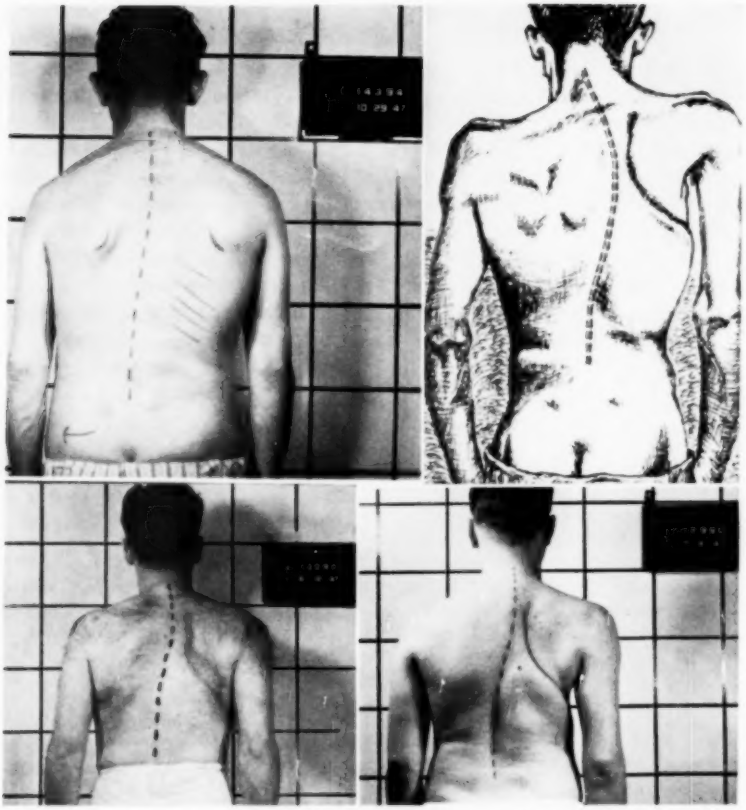

FIG. 5. (Upper left) A non-thoracoplasty patient with a scoliosis convex to right, due to a left fibrothorax. Characteristic changes accompanying scoliosis are present:

(a) head and neck deviated laterally to left

(b) high right shoulder girdle

(c) lateral prominence and posterior rotation of right thorax

(d) lateral prominence and anterior rotation of left pelvis.

FIG. 6. (Upper right) Possible skeletal changes resulting from thoracoplasty:

(a) deviation of head and neck towards the nonoperated side

(b) elevated and anteriorly displaced shoulder girdle on the operated side

(c) lateral curvature of the cervical-dorsal spine convex towards the operated side

(d) lateral prominence of the thorax on the operated side, often associated with rotation posteriorly

(e) lateral prominence, often combined with anterior rotation, of the pelvis on the contralateral side.

FIG. 7. (Lower left) A 27 year old patient with a 3 stage, 7 rib resection. Patient is of muscular build and quite proud of personal appearance.

FIG. 8. (Lower right) A 25 year old patient with a 4 stage, 8 rib resection. (Fourth stage included a revision and resection of the eighth rib.) Head and neck are straight and the shoulders level, with the lateral curvature fairly well compensated and the body symmetrically aligned.

which may be considered a flexible rod, it is normally bent or curved in the anteroposterior plane. If a bend in the lateral plane is imposed upon it, it will cause the spine to twist on itself and the twisting will take place most markedly in the area which permits the freest rotatory movement, the dorsal spine, When, for any reason, the spine habitually assumes this position of bending in two planes at the same time, certain structural changes take place, the most pronounced being a lateral curvature of the spine with vertebral rotation towards the convexity of the curve.

Accompanying the lateral curvature of the spine are certain characteristic skeletal changes. The rotation of the vertebral bodies towards the convexity of the lateral curve carries with it the thoracic cage, causing it to bulge laterally and posteriorly. The shoulder girdle on the convex side of the curve will usually be elevated and the head and upper cervical spine will tend to counterbalance by tilting slightly towards the high shoulder girdle. Compensatory changes are often evident lower in the spinal column, characterized by a laterally prominent and anteriorly rotated pelvis on the side contralateral to the prominent thorax (figure 5). These are the most prominent skeletal changes associated with scoliosis and they are to a variable degree what is seen in postthoracoplasty patients.

The direct cause for the scoliosis resulting from thoracoplasty is a mechanical imbalance created by the traumatization and weakening of the trunk muscles on the operated side and by the rib resection. In a seven rib resection, with the transverse processes removed, a number of muscles lose their points of origin, some their insertions, and others both their origins and insertions. Among the latter group of muscles are the intercostals which ordinarily exert a balancing force on the rib cage and indirectly on the spinal column. The net result is a lateral bending of the spine towards the stronger, nonoperated side.

Scoliosis was a common finding in all our thoracoplasty patients, as seen on the chest roentgenograms and on the photographs with spinal markings. Not always was the scoliosis evident to the eye from examination alone. Some patients, except for the scar, showed little outward manifestations of the thoracoplasty. In these cases the scoliosis was of slight degree and the outer integument covered over quite well the underlying skeletal structure, giving the appearance of a symmetrical body. Most of the patients, however, showed varying degrees of skeletal deviations, depending upon the severity of the scoliosis.

The first sign of scoliosis, as observed on the chest roentgenograms, is evident after the first stage of surgery in the cervical and upper dorsal region. The lateral curvature resulting from thoracoplasty is always convex to the operated side (figure 6).

After the first stage there may be a noticeable elevation of the shoulder girdle on the operated side with the arm adducted closely to the thorax. An elevated shoulder girdle on the convex side of a scoliosis is quite common. It may be exaggerated because of the pressure and bulk of the compression chest bandage. The upper trapezius, pectoralis major, and latissimus dorsi are often contracted; probably a reflex attempt on the part of the body to splint and protect the operated area. Parts of these muscles are also involved in the surgical procedure which is undoubtedly a cause for their increased tension.

As the stages of surgery progress, there is often a noticeable increase in the lateral curve in the cervical and dorsal regions, as noted on the chest roentgenograms. On clinical examination the remaining ribs on the operated side will often show greater angulation laterally and they may also be rotated posteriorly, depending upon the severity of the scoliosis. The pelvis on the contralateral side is prominent laterally and may show a rotation anteriorly, the latter indicating a compensatory lumbar curve (9, 11).

Viewed posteriorly in the standing position, the head and cervical region deviate towards the nonoperated side and the trunk and shoulders appear to be displaced laterally towards the operated side, at an oblique angle (figure 6).

With or without the benefit of physical therapy, the scoliotic changes seem to take place within a short time, starting soon after the first stage and are virtually completed shortly after the last stage. To what extent physical therapy can minimize the scoliosis has not as yet been determined. However, the scoliosis is not a progressive condition. Chest roentgenograms taken soon after the last stage compared with those taken a year later show no appreciable change in the spinal deviation.

The chest roentgenograms available to us showed only the lower cervical and entire thoracic spine. From these films it was noted that the apex of the lateral deviation was usually somewhere in the area of the fourth to sixth dorsal vertebrae. There was undoubtedly a compensatory curve lower in the spine in many of our patients, as evidenced by external pelvic alterations.

Shoulder Girdle Changes

Skeletal: It has already been noted that accompanying scoliosis there is usually a slight elevation of the shoulder girdle on the operated side. The elevation may be temporarily increased by the compression bandage and by contracted muscles reflexly splinting the operated field. The shoulder girdle may also be forced into a high position by a "hanging up," as the patients express it, of the scapula on the uppermost intact rib. This may occur after the removal of five to seven ribs and is common after the second stage, less common after the third. The uppermost unresected rib forms a shelf structure and the inferior angle of the scapula comes to rest upon the intercostal muscles which are in intimate contact with the shelf. The scapula at rest or during movement may cause mechanical irritation and pain, and the patient may elevate the girdle still higher to prevent the irritation. This phenomenon is often transitory in nature, subsiding after the next stage of surgery. When no more stages are contemplated and the irritation persists, a partial scapulectomy may be done in which the distal half of the scapula is excised. The present practice is to do the partial scapulectomy with the last stage when it appears that the inferior angle will be a hindrance to comfort and shoulder girdle functioning.

Occasionally the shoulder girdle persists in its elevated position even after the underlying cause is relieved. Alexander (1) attributes this to "organization of fibrous tissue in the field of operation beneath the scapula."

With an elevated shoulder girdle one usually finds a deepening of the supraclavicular fossa.

Another common finding is an anterior displacement of the shoulder girdle on the operated side (figure 10). The depression of the chest wall, observable anteriorly and posteriorly (figures 11, 16), created by the resection of ribs, permits the scapula to move forward into the decostalized area, carrying with it the clavicle and humerus. This forward displacement seems to place the scapular muscles at a mechanical disadvantage in certain of their movements, especially adduction.

Some degree of shoulder girdle elevation on the operated side was evident in many of our patients. The anterior displacement of the girdle, when noted, was

FIGS. 9, 10, 11. A 41 year old patient, who had a 2 stage, 7 rib resection at another institution, presents several interesting points:

FIG. 9. (Left) Shows a mild, well compensated lateral curvature with a slightly elevated right shoulder girdle. Patient's history revealed a preoperative spinal curvature convex to left in dorsal region, and a postoperative wound infection after second stage, necessitating strapping of arm to side for about six weeks. When patient reported for convalescent care he displayed tightness of pectoralis major and latissimus dorsi on right, with limitation of glenohumeral joint in flexion, abduction, and external rotation. Patient also complained of pain in region of right inferior angle of scapula, which was probably mechanical irritation between the latter and the eighth rib and possibly the cause for the elevated shoulder girdle on right side. The preoperative curvature convex to left now appears as a mild right cervical-dorsal, left dorsal-lumbar curve.

FIG. 10. (Centre) A lateral view of same patient showing forward displacement of shoulder girdle on operated side.

FIG. 11. (Right) Anterior view of same patient showing depression in right infraclavicular region due to resection of ribs, and a deepening of the supraclavicular fossa.

little influenced by the exercise program and seemed more a natural consequence of the surgical procedure.

Muscle function changes: After each stage the movements of the humerus away from the body are somewhat limited beyond a right angle. The contracted adductors, the pectoralis major and latissimus dorsi, limit the range of movement. As treatment continues, greater range is gradually attained.

A phenomenon frequently observed in those who had had three or more incisions through the trapezius, was a noticeable movement of the scapula upward and away from the body when the arm was abducted (figure 14). The superior angle of the scapula would rise above the outline of the shoulder and the vertebral border move somewhat posteriorly away from the chest wall. This is similar, but

FIG. 12. (Upper left) A 24 year old patient with a 2 stage, 5 rib resection. The left shoulder girdle is quite noticeably elevated, almost obliterating the normal neck contour. Inability to depress the shoulder girdle is due to the scapula sitting on the shelf formed by the sixth rib. Glenohumeral movements limited to 90 degrees in flexion and abduction.

FIG. 13. (Upper right) Same patient as in figure 12, four weeks after a partial scapulectomy was performed. Left shoulder girdle has returned almost to a level position and the neck lines are greatly improved in appearance. Glenohumeral movements are now freer with some pain persisting in the upper reaches of abduction.

FIG. 14. (Lower left) Same patient as in figures 12 and 13, with arms abducted to a right angle. Note elevated superior angle of scapula and posterior protrusion of vertebral border of scapula, left, indicating weakened trapezius.

FIG. 15. (Lower right) Same patient as in figure 14, with arms abducted beyond right angle. Arm on operated side has moved towards flexion and is limited about 40 degrees short of full abduction. Arm can be moved passively to full range.

to a lesser degree, to what Wright (12) noted in a case of paralysis of the trapezius muscle. In the case of the thoracoplastic patient, it represents a weakened trapezius. The movement of flexion of the glenohumeral joint elicits the same reaction of the scapula. As the movement of abduction continues beyond a right

angle, in these patients, the arm tends to move in the direction of flexion, and active abduction may be limited twenty to thirty degrees, and sometimes more (figure 15). Passively the arm can usually be moved to the completion of full range. The serratus anterior may share to some extent in the disturbed functioning of this movement since it acts on the scapula in conjunction with the trapezius. One of our surgeons has noted that the trapezius frequently is adherent to the scar of the deeper muscles and of the subcutaneous incision. It is his opinion that this may be a cause for the disturbed functioning of the trapezius.

In spite of the limitation of shoulder movements in the upper ranges, when they are tested routinely several months after the last stage of surgery, they display good or normal strength as compared with the nonoperated glenohumeral joint.

The rhomboideus minor and major muscles often show up their weakness in those movements in which they participate, especially when the movements are resisted. Normally one of the functions of the rhomboidei, together with the lower fibers of the trapezius, is as a stabilizer of the scapula in adduction or extension of the humerus. As a result of surgical incision during each stage the stabilizing action is impaired and the corresponding glenohumeral movements are weak and unsteady. Moreover, adduction of the scapula, a prime movement of the rhomboidei, is similarly involved.

Commonly associated with an elevated shoulder girdle are contracted upper fibers of the trapezius.

Patients often complain of a sharp pain or a persistently dull pain, aggravated by certain shoulder movements. The site of pain may be in the area of the shoulder joint, or along the medial or lateral aspect of the arm, or intercostally, or at the line of incision. Pain may be directly attributable to the section of some small nerves during surgery and it persists for variable lengths of time.

Factors Related to the Degree of Scoliosis and Concomitant Skeletal Deviations

From the start we have been particularly impressed by the difference between our patients in their external physical appearance after having been subjected to surgery. The question arises, "Why is the cosmetic result better in one patient than it is in another?" Rather briefly and inconclusively we shall consider those factors which in our opinion seem pertinent.

Exercise program: The exercise program has three main purposes: (a) maintenance of full range of active motion of the shoulder girdle on the operated side; (b) maintenance of muscle tone in the surgical area; (c) preservation of a symmetrical bodily alignment.

Barring complications which limit physical activity, such as wound infection, cardiac dysfunctioning, or spread of the disease, the exercise program will usually accomplish the first two objectives. At least the two objectives will be attained to the point that a degree of useful functioning sufficient for every day purposes will be present. Concerning the third objective, the preservation of a symmetrical bodily alignment, there are probably other factors which affect the end result, and these factors will be taken up in turn. But we must assume in all cases that

the objectives can be attained if we are to obtain the maximum results from physical therapy. The minimization of the skeletal deviations, by instruction in proper bed positioning, is more effective than the later attempt at correction. It is estimated that it requires about three weeks for the detached muscles to reattach themselves, and about four months for the ribs to regenerate. During this time, which means between stages and for about four months following the last stage, the patient needs to be constantly reminded and assisted in keeping the body in good alignment. And the same is true when the patient becomes ambulant.

Age: At first it seemed that the younger patients, particularly those under 25 years of age, developed a greater degree of scoliosis than the older patients. But this was found not to be true. Our youngest patients were 21 years old. At another institution we visited, where there were patients younger than 21, it was the opinion of the staff physicians that the scoliosis was greater in this younger age group, although older patients may and do develop the condition to a similar degree.

Cleveland (2) studied a series of 6 children with thoracoplasty and compared them to a typical adult thoracoplasty patient. The children (average age 14 years) developed a lateral curvature of 25 to 30 degrees one year postoperatively, and the adult, age 25, showed a curvature of 13 degrees at nine months postoperatively. The adult displayed about the same degree of spinal deviation at two weeks postoperatively as at nine months, while the curvature of the children tended to increase up to nine months to a year postoperatively and then remained stable. One striking exception occurred in a 12 year old patient who progressed to a 73 degree dorsal curve over a period of twenty-one months. The author states that "the amount of deformity to be expected will vary directly with the potential growth remaining in the spine."

Alexander (1) perhaps furnished an additional clue when he stated, "the anatomical changes tend to be greater in young persons with elastic chests and undeveloped muscles than in well-developed adults whose chests are relatively rigid and stable. Poorly developed adults react much as children do."

Nature of Surgery: It can be stated with reasonable safety that a one stage thoracoplasty will show less skeletal defect than a thoracoplasty of two or more stages. The more ribs resected, together with the removal of the transverse processes, usually makes for a greater lateral curvature.

Seven ribs may be resected in two or three stages. The number of stages will influence the strength of the musculature involved, especially those muscles which are incised at each stage.

The excision of the vertebral transverse processes makes for a better collapse of the lung, but at the same time it seems to increase the scoliosis. At two other institutions we have noted that the transverse processes are not disturbed, or are only partially removed, with apparent lessening in the degree of scoliosis. The small intertransverse muscles and ligaments and the muscles of the deep layer of the back which are attached to the transverse processes probably exert an important stabilizing effect on the spine.

Recently the surgical approach has been modified in selected cases. The technique is referred to as a muscle split thoracoplasty. It is used on those patients who have a cavity high in the apex of the lung and who do not require the resection of more than five ribs. The first stage incision is performed on a line parallel to the fibers of the mid-trapezius and the rhomboidei (figure 23). These

FIG. 16. (Upper left) A 28 year old patient with 3 stages, 7 ribs resected. A long, thin body often accentuates the existing deviations. Photograph illustrates depression of upper chest wall posteriorly.

FIG. 17. (Upper right) A 46 year old patient who has had 3 stages, 7 ribs resected. The heavier, muscular patients often cover over well the existing skeletal deviations.

FIG. 18. (Lower) A 28 year old patient who went through 2 stages, 5 ribs resected, and also a partial scapulectomy. This illustrates a heavy set, symmetrically aligned patient.

muscle fibers are separated, rather than cut transversely, and the posterior sections of the upper five ribs are removed. The second stage incision is done along the mid-axillary line (figure 24) and the anterior segments of the first five ribs are resected. This procedure is less traumatizing and less destructive to the musculature of the shoulder girdle usually involved in a thoracoplasty. It makes for

a better functional end result. What effect it has on the scoliosis has not as yet been determined. The patients on whom this procedure has been used are not included in the original 60 patients we have studied.

Condition of spine prior to surgery: Among our patients were a few who, previous to surgery, had developed a fibrothorax, and the thorax was contracted towards the same side. This pulling over of the trunk, maintained over a period of time, caused a scoliosis convex to the opposite side (figures 5, 19). It has already been noted that the thoracoplasty brings with it a lateral curvature convex towards the operated, affected side. When the two processes are combined, the fibrotic scoliosis and the thoracoplasty scoliosis, the result is a mild, compensated curve, convex to the operated side in the cervical-dorsal region and convex to the opposite side in the dorsolumbar regions (figures 9, 20). The thoracoplasty tends

FIG. 19. (Left) Preoperative photograph of a 26 year old patient showing a curvature of spine, convex to left. Right fibrothorax has caused the trunk to bend laterally to the right.

FIG. 20. (Right) Same patient as in figure 19, after a 3 stage, 7 rib resection. The lateral curvature of the spine has changed to a mild right cervical-dorsal, left dorsal-lumbar curve, and the patient is fairly well aligned.

to counteract the fibrotic contracture, minimizing the lateral curvature. The same is true in cases of empyema.

Morphological type: We have already quoted Alexander's statement to the effect that adults with poorly developed muscles tend to show greater anatomical changes than do well-developed individuals. In general, we have noted that the thin, asthenic individual shows up poorer than the stocky or heavy set, muscular one. While there may not always be a greater degree of scoliosis and accompanying changes in the thin patient, there is quite often an accentuation of the existing deviations (figures 16, 21). The thin patient's bodily contours are more sharply defined, whereas the heavy set patient fills in and covers over the hollows and prominences created by surgery (figures 17, 18).

Personality: It would be altogether too easy to say that one patient attained better results because he was more cooperative than one who did not come out too well, but there did seem to be some relationship, in a few patients, between

the personal factor, expressed in terms of personal pride in carriage and bearing, and a good outward appearance (figures 7, 8). Conversely, there were several patients who expressed interest only in getting rid of their tuberculosis and did not particularly care how they looked after surgery; these did not show up too

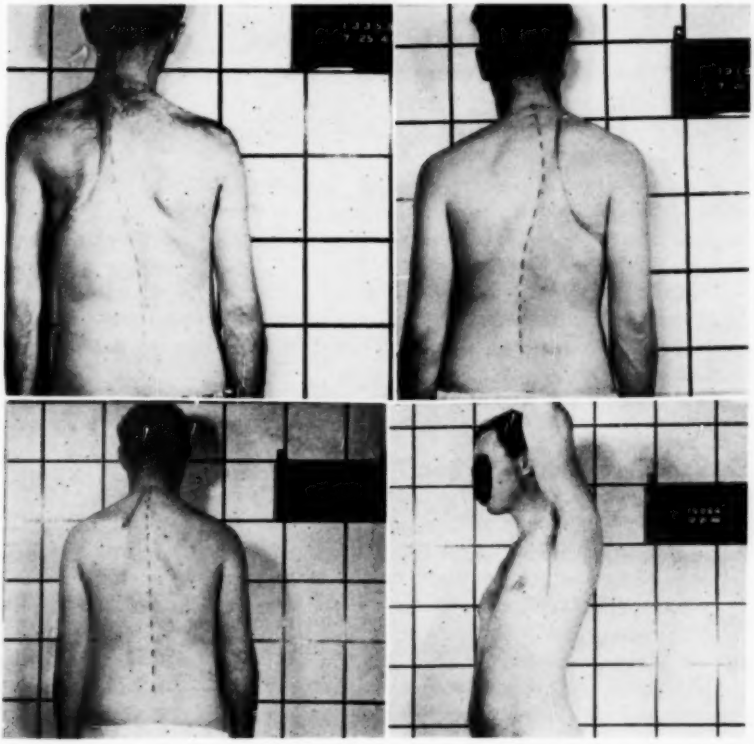

FIG. 21. (Upper left) A 29 year old patient who received a 3 stage, 7 rib resection. Of asthenic build, this patient did not care too much about appearance.

FIG. 22. (Upper right) A 25 year old patient with a 3 stage, 7 rib resection. Somewhat heavier than the patient in figure 21, this patient was similarly unconcerned about his posture.

FIG. 23. (Lower left) Shows first stage incision of a muscle split thoracoplasty. Patient is 27 years old and has had 5 ribs resected in 2 stages.

FIG. 24. (Lower right) Same patient as in figure 23, showing the second stage incision of a muscle split thoracoplasty. Incision scars have been darkened in both photographs.

well (figures 21, 22). They just did not bother to exert the effort necessary to maintain good bodily alignment in bed and out of bed, whereas those who took pride in their posture were constantly aware of it and that in itself was sufficient to assure full cooperation.

These statements are based only on those patients from whom we received

some positive pronouncements of active concern or of passive acquiescence, and the number was relatively small in either case. The same process may have been at work in other patients who gave no indication one way or the other.

It is difficult to separate the personal factor, or any one of the factors, from the others which influence the end result of the thoracoplasty.

SUMMARY AND CONCLUSION

1. Sixty postthoracoplasty patients were observed during a one year time in a Veterans Hospital for tuberculous patients.

2. The observable changes which resulted from thoracoplasty were classified under two headings:

(a) scoliosis with concomitant skeletal changes of the head and neck, the shoulder girdle on the operated side, the thorax, and the pelvis

(b) skeletal deviations and changes of muscle function of the shoulder girdle on the operated side.

3. An attempt was made to explain the differences in external appearance resulting from thoracoplasty on the basis of six factors: exercise program; age of patient; nature of surgery; condition of spine prior to surgery; morphological type; and personality.

SUMARIO Y CONCLUSIONES

La Fisioterapia en la Postoracoplastia. Un Año de Notas y Observaciones

1. Sesenta enfermos posteracoplásticos fueron observados durante un año en un Hospital de Veteranos para tuberculosos.

2. Las alteraciones observables debidas a la toracoplastia fueron clasificadas bajo dos encabezados: (a) escoliosis con alteraciones esqueléticas concomitantes de la cabeza y la nuca, el anillo del hombro del lado operado, el tórax y la pelvis; (b) desviaciones esqueléticas y alteraciones de la función muscular del anillo del hombro del lado operado.

3. Trátase de explicar las diferencias en el aspecto externo debidas a la toracoplastia a base de seis factores: plan de ejercicio; edad del enfermo; naturaleza de la cirugía; estado del raquis antes de la intervención; tipo morfológico; y personalidad.

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CONCERNING THE LOCATION OF PULMONARY INFARCTION[1]

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Despite the voluminous literature available on pulmonary infarction, the site in the lung most often infarcted has been commented upon infrequently. White (1) and others (2, 3) have emphasized that pulmonary infarcts are usually found in the right lung. While this opinion is the most prevalent, there is need for re-evaluation of factual information and reorientation of physiological aspects. Herein lies the purpose of this report. An appraisal of the location of pulmonary

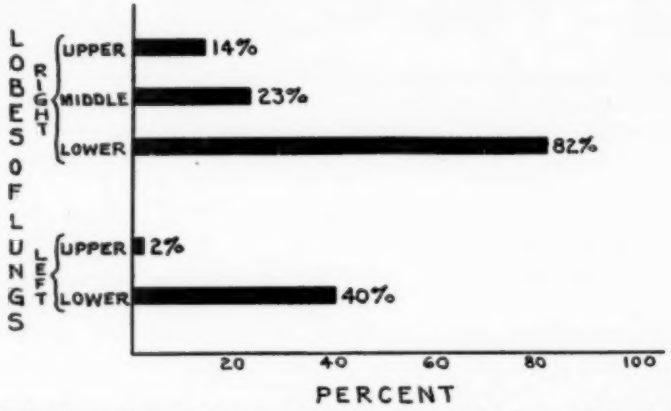

FIG. 1. Incidence of specific lobar involvement in 100 cases of pulmonary infarction (multiple involvement in 60 per cent).

infarction should be accompanied by an explanation of the increased frequency of a particular site of involvement.

OBSERVATIONS

The frequency of involvement of each lobe of the lungs was investigated in 100 cases of pulmonary infarction found at routine necropsy at the Metropolitan Hospital in New York City. Examination of figure 1 reveals that in 82 per cent of the cases the infarct was located in the right lower lobe. The right upper lobes and middle lobes contained relatively few of the infarcts. There were more infarcts in the left lower lobe than in either the right upper or middle lobes. Nevertheless, the number in the left lower lobe was less than one-half that found in the right lower lobe. A total of 119 infarcts were found on the right side while a total of 42 infarcts were present on the left.

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DISCUSSION

The explanation for the right-sided predominence of pulmonary infarction is presumably related to the presence of congestion. Zahn (4) in 1897 demonstrated that pulmonary infarction was more likely to occur in rabbits after embolization in the presence of passive congestion. Karsner and Ash (5) studied the role of stasis in pulmonary infarction in 1912. In a noteworthy paper it was shown that hemorrhagic infarcts appeared after the ligation of pulmonary arteries when the veins likewise were subjected to ligation. They concluded from the study that simple embolism does not produce pulmonary infarction. Stasis is the necessary corollary and, moreover, the greater the stasis the earlier will infarction occur.

Patients with cardiac disease who are either in acute or chronic failure provide an excellent means for the clinical study of the association of passive congestion and pulmonary infarction. Examination of the protocols of 100 consecutive necropsies of patients with cardiac disease revealed that 33 per cent had demonstrable infarcts. This is in agreement with White (3) and Hinds (6) who state in recent reports that the incidence of pulmonary infarction in cardiac patients is approximately 30 per cent.

The importance of stasis in the genesis of infarction following pulmonary embolism was investigated recently from an experimental standpoint by Moses (7). Pulmonary emboli were produced by inserting into the jugular veins of rabbits wool yarn previously soaked in defibrinated blood. Compression of the thorax, producing congestion, was accomplished with wide rubber bands. A control series of rabbits not subjected to compression of the thorax was likewise studied. In the latter group, bland embolism without infarction was noted at autopsy. When stasis and congestion were produced, hemorrhagic infarcts developed. These observations stressed the importance of preventing circulatory stasis in order to prevent pulmonary infarction.

Evidence of a confirmatory nature is presented by examination of the pulmonary artery for emboli in the absence of infarction and congestion. It has been estimated by Belt (8) that only 50 per cent of emboli cause infarction. In the absence of predisposing factors for infarction, embolization may not produce pathological changes in the lungs.

Thus, congestion has been shown to be a factor of the greatest importance. Study of this alteration of normal physiology affords a possible explanation for the localization of most pulmonary infarctions to the lower lobes and, more particularly, to the right lower lobe. The influence of gravity in the upright position is undisputed in the causation of basal congestion. Significant factors governing pulmonary arterial circulation were discussed by Dock (9) in his discussion of the apical localization of tuberculosis. The relation between the right ventricular pressure of 20 to 25 mm. of mercury systolic and 0 diastolic, and the intrathoracic pressure of -5 to -10 causes an effective pulmonic arterial pressure of 25 to 30 systolic and 5 to 7 diastolic. The mean pressure, Dock points out, is 15 to 18 mm. of mercury, or, in terms of a column of blood, would be 19 to 23 cm. This pressure is sufficient to cause an active circulation of blood in the lower portions of the lungs but the apices, which are as far as 30 cm. cephalad

to the center of the right ventricular cavity, presumably cannot be effectively supplied unless the dynamics are altered by putting the patient in a horizontal position. It would follow that a sluggish circulation postoperatively in cardiac decompensation, or in a confining illness, would primarily cause congestion in the lower lobes. With the explanation of hemodynamics given, it is inferred that relatively little blood flows through the upper lobes since patients are seldom completely recumbent. Therefore, the low incidence of infarction in the upper lobes might easily be explained as a consequence of the low blood supply and the resulting lesser degree of congestion which occurs in this area.

The problem of the predominence of right-sided infarction remains unexplained but it is of interest that the congestion of the right lung is usually more severe and appears earlier than on the left. This is demonstrated in cases of cardiac decompensation with hydrothorax. The fluid is almost exclusively situated on the right side. Apparent exceptions in which hydrothorax has been noted clinically on the left have been explained at necropsy. Adhesions of the visceral and parietal pleura in these cases have obliterated the potential pleural cavity on the right preventing the accumulation of fluid (3). Many hypotheses have been suggested to explain the high incidence of right hydrothorax but pulmonary engorgement is a *sine qua non* of all explanations (10). Thus an understanding of the pathogenesis of right hydrothorax is of utmost importance in any discussion of the predominence of infarction of the right lung.

Increased stasis especially on the right side is produced in heart failure as a consequence of enlargement of the right atrium and subsequent compression of the right pulmonary veins. These veins lie in close apposition to the right atrium and superior vena cava. While compression of the azygous system is important in the genesis of hydrothorax, it is not of significance in pulmonary congestion since the veins of the parietal pleura drain into this system but not the veins of the visceral pleura. It is pointed out by Dock (11), reviewing the anatomical factors in right hydrothorax, that patients with cardiac decompensation lie in the preferred right lateral recumbent position, causing a higher venous pressure in the right lung. The blood from the right lung must be lifted to the level of the left atrium in this situation while drainage from the left lung is aided. Congestion in the right lung is promoted greatly by this position. In the patient who develops pulmonary infarcts in the absence of cardiac failure, these factors may not be as pertinent.

The flow of blood through the pulmonary artery has received attention. Scherf and Schönbrunner (12) introduced masses of radio-opaque substances into the femoral veins of dogs. A majority of these masses were seen to lodge in the lower right lobe. In 2 of their experiments, 3 of 5 masses passed to the identical vessel. This work arouses speculation as to whether the pulmonary arteries may influence preferential flow of emboli to the right lower lobe. Text books of anatomy (13, 14) agree that the right branch of the pulmonary artery is larger and longer than the left. Small differences in diameter in these arteries may cause great differences in the volume flow of blood since the physical principle holds that the quantity of a fluid passing through a tube per unit of time is proportional

to the fourth power of the diameter (15). Strict physical laws cannot completely govern the division of pulmonary arterial blood flow because of such factors as variability of diameter, distensibility of the arteries, and the angles at which the arteries branch from the main pulmonary artery. Consideration of the influence of the greater diameter of the right pulmonary artery, however, may afford an explanation of the fact that emboli seem to lodge more frequently in the right lung.

The relation of the dual circulation of the lung to the problem is speculative for the most part. Consideration of the anatomy, physiology, and pathology of the bronchial artery may contribute to the explanation of the predominence of right-sided pulmonary infarction. As a rule, there is only one bronchial artery to the right lung which arises from either the first aortic intercostal artery or from the left bronchial artery. In contrast, on the left side there are two bronchial arteries arising from the thoracic aorta (13, 14). The blood supplied through the bronchial arteries to the right lung is thus not as great as to the left lung. This quantitative difference is of questionable major importance but it may be of significance as a contributory factor in the localization of pulmonary infarction to the right lung.

In various pathologic conditions, the bronchial arteries may increase in size and carry a considerable portion of the blood to the lung. Virchow (16) first demonstrated that after obstruction of a pulmonary artery there was an increased bronchial artery development. By injecting radio-opaque substances into the bronchial arteries of cadavers and then examining the state of the arteries in various diseases, Wood and Miller (17) discovered that in lesions of the pulmonary vascular tree and in cardiovascular diseases, numerous bronchopulmonary artery anastomoses developed. The anastomoses widened in all cases of increased pulmonary venous pressure. Therefore, where the lung is predisposed to infarction by being severely congested, the bronchial artery supplies an increased portion of the blood to the lung. It is possible that, because of the additional bronchial artery, the circulation to the left lung is more strongly fortified than to the right. Obstruction of a smaller branch of the pulmonary artery on the left might not result in infarction while an embolus to a similar vessel on the right would result in the pathologic changes of infarction.

The development of the bronchial artery progresses further in cases which are chronic. Wood and Miller found that in cases of far advanced pulmonary tuberculosis the bronchial artery was greatly enlarged. The increase of blood flow through the bronchial arteries in advanced tuberculosis would lead one to expect a low incidence of pulmonary infarction. To compare the frequency of pulmonary infarction in tuberculosis to our general incidence of approximately six per cent of necropsies, protocols of 200 cases of advanced pulmonary tuberculosis were studied. In this group, not one case of pulmonary infarction occurred. Recently Fox, *et al.* (18) studied 2,182 postmortem examinations in a hospital devoted completely to the treatment of tuberculosis. In this large series, only 22 cases (one per cent) of pulmonary infarction were diagnosed. They remark that this is a strikingly small number in an institution where bed rest is a funda-

mental therapeutic procedure. They explain the rarity of infarction in three ways: (*1*) the relatively young age group of the patients; (*2*) the exceedingly small number of patients in cardiac failure; (*3*) the predominant pathologic finding of thrombophlebitis which is said to embolize less frequently than phlebothrombosis.

There are undoubtedly other factors which influence and are responsible for this low incidence in tuberculosis. The changes in the bronchial arteries, however slight, invite speculation. If alterations in these vessels are responsible, in part, for a low incidence of infarction in tuberculosis, other conditions may also be effected similarly. Following this reasoning, the superior distribution of the bronchial arteries to the left lung may prevent so frequent infarction as on the right, where only one bronchial artery is present.

A better understanding of the pathologic physiology of pulmonary infarction and the reasons for its more frequent occurrence in the right lower lobe is essential for a rational approach to prevention of the phenomenon. With more attention focused on the reversible physiologic factors that are involved in the pathogenesis of infarction, necrosis of the pulmonary parenchyma might be avoided in some instances.

SUMMARY

It is shown that pulmonary infarction occurs most frequently in the right lower lobe. For many years, stasis in the pulmonary vascular system has been recognized as the primary predisposing factor in the development of infarction. By clinical and experimental investigation, confirmation of this fact exists. Increased congestion in the right lower lobe seems to account for the prevalence of infarction here. The pathological physiology which causes more pronounced stasis in this lobe has been reviewed. Other factors which may be of significance in the predominance of right lower lobe infarction have been considered. Among these are the preferential flow of emboli to the right lower lobe and a comparative decrease in bronchial artery blood supply to the right side. The rarity of pulmonary infarction in tuberculosis is emphasized and explained in so far as it may have bearing on understanding the genesis and localization of pulmonary infarction in the right lower lobe.

SUMARIO

Sobre la Localización del Infarto Pulmonar

Es sabido que el infarto pulmonar sobreviene más frecuentemente en el lóbulo inferior derecho. Por muchos años, ha sido reconocido que el éstasis del aparato vascular pulmonar es el factor predisponente primario en la producción del infarto, y así lo han confirmado las investigaciones clínicas y experimentales. La hipercongestión del lóbulo inferior derecho parece explicar la frecuencia del infarto allí. Después de repasar la patofisiología que ocasiona un estatismo más pronunciado en dicho lóbulo, considéranse otros factores que pueden revestir importancia en el predominio del infarto del lóbulo inferior derecho. Entre los últimos figuran el paso preferencial de émbolos a ese lóbulo, y la comparativa

disminución de la circulación de la arteria bronquial al lado derecho. Recálcase la rareza del infarto pulmonar en la tuberculosis, explicándola en lo que pueda guardar relación con la comprensión de la génesis y localización del infarto en el lóbulo inferior derecho.

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FACTORS AFFECTING THE IN VITRO CYTOLYSIS OF WHITE BLOOD CELLS BY TUBERCULIN[1, 2]

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INTRODUCTION

Since Koch first introduced tuberculin as a "cure" for tuberculosis, much attention in the clinic and laboratory has been devoted to the role which the tuberculin type of allergy plays in human tuberculosis. Although a similar type of tissue reaction occurs following sensitization to substances from many other bacteria or parasites and has been studied in the field of sensitization to simple chemical compounds (1), the tuberculin type reaction still is taken as the prototype of the delayed types of tissue hypersensitivity.

The now classic tissue culture studies of Rich (2, 3, 4, 5) have shown that the tuberculin reaction is in some way related to the white blood cell types of the host. *In vitro* cultures of splenic explants from tuberculous guinea pigs, grown in plasma from normal animals, are destroyed by amounts of tuberculin nontoxic for normal animal tissue cultures. On the other hand, explants from anaphylactically sensitized animals are not damaged when exposed to homologous immune serum of sensitizing antigen (6). More recently Landsteiner has shown that the delayed type of sensitivity is transferable to a normal host when cells, but not serum, of a sensitized animal are used (1). Chase (7) and others (8, 9, 10) have extended this technique to the tuberculin reaction itself, thus still further implicating the white blood cell and not a serum antibody as the mediator in the tuberculin type reaction.

When the effect of tuberculin on white blood cells is studied in fluid suspensions rather than in the fixed cell masses of the tissue culture techniques, a similar cytotoxic effect of tuberculin is observed (11). Although this destructive effect of tuberculin on white blood cells has been noted on selected cases of human tuberculosis (12), little is known concerning the clinical conditions under which this phenomenon may be present. The present report is a study of a larger group of tuberculous subjects, as well as persons with other acute illnesses, by means of such an *in vitro* tuberculin cytolysis procedure. The findings in these patients constitute the body of the report which follows.

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MATERIALS AND METHODS

For the sake of systematization, the patients studied have been grouped according to the accuracy of diagnosis and severity of illness. By these criteria, the subjects studied fall into five groups:

1. Active tuberculosis with systemic manifestions (fever, weight loss, cough, expectoration); clinical and roentgenographic evidence of disease and/or recovery of tubercle bacilli on culture.
2. Active tuberculosis with little or no systemic manifestations (without toxic effects); clinical and roentgenographic evidence of disease.
3. Obscure febrile illnesses with a self-limited course; positive PPD cytolysis test during acute phase of illness.
4. Other acute febrile diseases.
5. Normal subjects with and without a positive cutaneous tuberculin reaction.

Method

Technique: One tenth ml. of heparin (Liquaemin 10 mg. per ml. in 0.85 per cent NaCl) and 0.05 ml. of 5 per cent dextrose are drawn into a 2 ml. syringe. Two ml. of blood (total volume 2.1 cc.) are then withdrawn by venipuncture without stasis, and the blood and heparin promptly mixed in the syringe with the aid of a bubble of air. A PPD (Purified Protein Derivative of tuberculin) (13) solution is prepared by dissolving one 25 gamma tablet of PPD in 0.5 ml. of 0.85 per cent NaCl (not phosphate buffer)[5]. Old Tuberculin[6] 0.1 ml. of a 1:30 dilution may be used in place of PPD and will give comparable results (table 1).

Four tenths ml. of the heparinized blood is put in each of two 1.0 cm. diameter Kahn tubes which have been shortened to 4 cm. lengths for ease in white count pipetting and which have been coated with organosilicon (14) to diminish nonspecific cytolysis. One tenth ml. of PPD solution is added to one tube and 0.1 ml. saline to the other. The tubes are immediately shaken by hand for three minutes and a white blood count is done with a mechanical pipette filler[7] and calibrated pipettes. Fifteen squares on 2 chambers of the standard hemocytometer slide are counted. These two counts are the five minute counts indicated in the tables. The tubes are stoppered and rolled slowly in an incubator at 37° C. for one hour. They may be shaken continuously during this time if a shaker is available or at the end of an hour should again be shaken by hand for three minutes before recounting. Adequate terminal shaking is essential for accurate counts. Likewise, a minimum constant speed of shaking the pipette after adding acetic acid, preferably by a mechanical shaker, is desirable. A positive cytolysis test will show a fall in the white blood count in the presence of tuberculin and not in the presence of saline. In the hands of careful technicians who follow these precautions scrupulously, the "technical error" can be below 5 per cent (table 5). Detailed data on the different groups studied are given to support this conclusion.

Clumping: When fresh white blood cells are placed in a noxious envirionment, the neutrophils, especially those of the sick patient, tend to clump together or adhere to surfaces. This reaction might well be expected since intravital dye morphological studies of white blood cells taken from patients with active tuberculosis show alterations in granular content and increased vacuolation (15). In specific tuberculin cytolysis, the clumping tendency observed is roughly proportional to the specific cytotoxic effect of tuberculin. Appropriate

[5] Phosphate or citrate ions will block specific tuberculin cytolysis.

[6] O. T. was dialyzed for six days against frequent changes of 0.85 sodium chloride and made up to a 1:30 dilution calculated on the basis of the original volume of crude O. T.

[7] Automatic suction apparatus, Clay Adams Company.

TABLE 1

Group I. *Active Tuberculosis*

Positive Cytolysis Test

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	CULTURE*	COMMENT
M. S.	2-22-48		−4.0	−29.5	−35.5	G+; S+	Acute exudative pulmonary tuberculosis
	3- 1		−4.5	−27.6	−23.1		
Ro. P.	5-24	3,590	−0	−33.4	−33.4	S+	Tuberculous bronchopneumonia
	5-26	4,200	−1.0	−46.5	−45.5		
	5-28	3,740	−4.0	−47.5†	−45.5		
	6-18	5,060	−2.7	−34.0†	−31.3		
	6-24	5,500	−3.1	−36.1†	−33.0		
	6-26	2,910	+0.7	−46.5†	−45.8		
	7-12						Streptomycin started
	7-22	5,570	+1.7	−20.4	−18.7		
	7-29	3,940	−2.1	−34.7†	−32.1		Poor response to streptomycin
A. B.	6-18	6,300	−1.8	−27.0	−28.8	Pl.fl.+	Acute pleurisy with effusion
	6-23	6,800	−0.5	−15.1	−14.6		
W. C.	6- 2	7,390	−1.0	−14.8	−13.8	S+; G+	Acute exudative pulmonary tuberculosis
	6- 4	8,600	−0.3	−19.9	−19.6		
Ri. P.	2-18	3,270	0	−2.2	−2.2	G−	Tuberculoma of lung
	6-12					G+	Tuberculoma with cavity
	9-28	9,360	−2.5	−15.6	−13.1	G+	3 months pregnant
	9-29	6,850	+0.7	−14.7	−15.4		
M. M.	9- 7	8,130	−0.7	−9.6	−8.9	S+	Acute exudative pulmonary tuberculosis, far advanced, tuberculous bronchitis and laryngitis
	9- 9	7,030	+1.0	−15.3	−14.3		
	10- 5	6,490	+0.5	−41.7†	−42.2		
	11- 5	8,700	−2.2	−35.3	−33.1		
H. K.	10-11	8,050	−4.1	−21.8	−17.7	S+	Acute exudative pulmonary tuberculosis, moderately advanced
	10-14	6,830	−0.7	−26.8	−26.1		
	10-14	6,800	−0.7	−22.8†	−22.1		
	10-16	4,870	−0.7	−14.5†	−13.8		
	11- 2	3,360	−1.1	−29.7†	−28.6		
	11-15	6,720	−2.0	−29.7	−27.7		
	11-17	4,560	−0.7	−21.7†	−21.0		
	11-22	5,960	0	−15.0†	−15.0		
G. C.	11- 9	7,840	−0.5	−25.7	−25.2	Biopsy+	Mesentery adenitis, tuberculous; rheumatoid arthritis, active
	11-10	8,560	−1.1	−31.8	−30.7		
	11-23	5,650	+0.7	−22.4†	−23.1		
T. D.	4-20	12,450	−5.6	−26.5	−20.9	G−	Acute pleurisy with effusion
	4-22	12,450	−3.4	−37.3	−33.9		
	10- 2	6,150	−1.0	+0.5	+1.5		Well

TABLE 1—*Continued*

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	CULTURE*	COMMENT
W. M.	6-25	6,490	−6.2	−38.0	−31.8	G−	Acute pleurisy with effusion
	6-29	6,530	+0.5	−17.4	−17.8	Pl.fl.−	
	7-11						Began streptomycin treatment
	7-14	7,470	−0.7	−2.4†	−1.5		
	7-22	6,580	0	+1.2	+1.2		
M. E.	6-22	6,510	−9.9	−36.7	−26.8	G−; S−	Acute exudative pulmonary tuberculosis
	6-25	5,180	−2.3	−16.8	−14.5		
	6-29	4,270	−1.5	−20.6	−19.1		
C. H.	6-29	15,000	−1.8	−26.0	−24.2	G−; S−	Acute exudative pulmonary tuberculosis
	7- 1	19,700	−16.2	−34.1	−17.2		
	7- 6	14,410	−0.5	−39.3	−38.8		
N. S.	7-15	4,660	0	−31.2	−31.2	G−; S−	Acute exudative pulmonary tuberculosis
	7-27	5,560	−2.3	−39.0†	−35.7		
	7-27	5,560	−0.6	−34.8	−34.2		
W. J.	5- 6	3,940	−1.6	−25.7	−24.1	G−; S−	Acute exudative pulmonary tuberculosis
	5-11	6,000	−4.6	−14.1	−9.5		
	5-14	8,490	−1.7	−25.2	−23.5		
L. C.	6-25	5,460	−1.7	−38.7	−32.0	G−; S−	Acute exudative pulmonary tuberculosis
	6-29	4,750	+2.0	−20.5	−22.5		
G. L.	11-16	6,170	−1.0	−32.2	−31.2	G−	Exudative pulmonary tuberculosis, minimal, active.
	11-17	5,190	−0.5	−22.7	−22.2		
	12- 1	5,070	+1.2	−4.1	−5.3		

* G—gastric aspiration cultured; S—sputum cultured; Pl.fl.—pleural fluid cultured.
† O.T.—See text.

tuberculin controls on normal white blood cells and antigen controls on the patient's blood with a streptococcus protein[8] indicate that this phenomenon is a part of the cytotoxic effect itself and not an artifact. A similar clumping tendency has been found in association with the alarm reaction to be discussed in this paper. This clumping tendency has been offset satisfactorily by keeping white cells under as nearly physiological conditions as possible. Adequate glucose is present, glassware is chemically clean, sterile saline suitable for intravenous use is employed, and tubes are stoppered to prevent shifts in pH due to evolution of carbon dioxide.

The cytotoxic effect of tuberculin takes place in 20 minutes to one hour and changes little thereafter. In a positive reaction, from 10 to 40 per cent of leukocytes are destroyed in this interval. In man the small mature lymphocytes and the neutrophils are the cells lost. If

[8] This material is obtained from beta hemolytic streptococcus by formamide extraction. It produces a delayed-type intracutaneous reaction in subjects who have recently had a streptococcal infection. It also causes a disease-specific *in vitro* cytolysis when used by the method described in this report. The details of its preparation and its relation to clinical disease will be presented in a separate communication.

their percentage fall is great in this period, a further fall may be anticipated. In general, however, counts done at 90 and 120 minutes agree closely with the 60 minute counts.

RESULTS

Active tuberculosis: In table 1 (Group I) there are listed a selected group of patients who have been studied during hospitalization for tuberculosis. Each

TABLE 2

Group II. *Active Tuberculosis*

Negative Cytolysis Test

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	CULTURE*	COMMENT
W. Mc.	6-8-48	6,240	−3.7	−1.0	+2.7	S−; G−	Pulmonary tuberculosis, minimal, active
	7-6	6,660	−3.7	−3.5	+0.2		
A. M.	7-7	4,530	−5.3	−0.7	−4.0	S+	Pulmonary tuberculosis, moderately advanced with cavitation
	7-8	4,020	+1.0	−3.0	−2.2		
M. G.	3-8	2,210	+5.5	+4.0	+1.5	G+	Pulmonary tuberculomas; pleural effusion; controlled diabetes mellitus
R. A.	9-7	6,770	−0.7	−0.7	0	S+	Pulmonary tuberculosis, moderately advanced
	9-9	5,120	−1.8	−1.5	+0.3		
O. F.	9-7	4,560	0	−0.9	−0.9	S+	Pulmonary tuberculosis, moderately advanced
	9-9	3,670	−1.7	+1.2	+3.9		
L. M.	9-7	6,390	−2.2	−7.0	−4.8	S+	Pulmonary tuberculosis, moderately advanced
	9-9	3,130	−0.7	−5.0	−4.3		
B. S.	9-21	7,650	+0.3	−0.4	−0.7	G+	Pulmonary tuberculosis, moderately advanced
	9-23	5,490	−1.5	−1.5	0		
E. S.	9-22	8,530	0	−1.8	−1.8	D+	Tuberculosis of spine with draining psoas abscess
	9-23	9,780	−0.6	0	+0.6		

* S—sputum cultured; G—gastric aspiration cultured; D—drainage cultured.

person ran a degree or more of temperature elevation and, in addition to the laboratory findings indicated in the table, appeared to be acutely ill. White cell studies were done two or more times on different days. It will be observed that PPD decrements[9] varied in the same and in different patients but were greater than 10 per cent in each individual. The sicker the patient, the greater the PPD

[9] PPD decrement is the difference between the per cent fall in white count in saline and in PPD solution.

TABLE 3

Group III. *Other Diseases*

Positive Cytolysis Test

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	COMMENT
A. M.	7- 8-48	5,520	+0.7	−23.6	−24.3	Post-sedation atelectasis and febrile bronchitis
	7- 9	4,850	+0.5	−32.7	−33.2	
	7-26	5,560	0	−6.1	−6.1	Recovered
M. W.	9-10	4,640	−8.5	−25.3	−16.8	Age 80; negative physical examnation and laboratory findings
	9-11	5,390	+2.0	−12.3	−14.3	
	9-13	6,380	−7.7	−18.7	−11.0	
A. C.	9-10	3,790	−9.5	−14.6	−5.1	Fever of unknown origin, 5 weeks
	9-11	5,850	+2.2	−13.8	−16.0	
	9-13	5,140	−1.4	−19.5	−18.1	Temperature normal 3 days after streptomycin treatment
	9-21	6,780	−4.2	−4.2	0	
W. B.						Myocardial infarction with congestive failure; mural thrombus and cerebral embolus
	9-30	11,100	0	−10.0	−10.0	−23.0 with Brucellergin
	10-1					One pint pus from iscial abscess drained 10-1 (E. coli, proteus, A. aerogenes)
	10- 4	8,400	−0.7	−8.2	−7.5	−44.2 with Brucellergin
H. O'C.	9-13	5,870	−2.1	−56.7	−54.6	Renal colic
	9-14	5,740	+1.4	−28.0	−29.4	
	9-16	4,880	+1.1	−35.2	−36.3	
	9-18	5,800	−2.3	−27.6*	−25.3	
	9-21	5,190	−1.5	−13.3	−11.8	
	10- 2	5,100	−2.2	−15.5	−13.3	
	10-11	3,870	0	−2.3	−2.3	
P. G.	10-24					Pulmonary infarct in an area containing calcified hilar lymph nodes
	10-27	7,450	−5.0	−8.2	−3.2	
	10-29	6,860	0	−21.4	−21.4	
	11-13	7,430	0	−26.1	−26.1	
	11-26	5,110	−1.0	−24.3	−23.3	
	12- 3	6,730	+0.3	+0.3	0	Recovered

* O.T.—See text.

decrement. On the other hand, the PPD decrement was below 10 per cent during relatively quiescent phases of the patient's course (R. P., M. M.) or coincident with obvious clinical improvement (T. D., W. M.).

In table 2 (Group II) are listed patients with active tuberculosis whose blood showed a negative cytolysis test with PPD. The lesions vary from minimal pulmonary tuberculosis (W. Mc.) through moderately advanced disease (A. M.) to a

TABLE 4

Group IV. *Other Diseases; no Alarm Reaction*
Negative Cytolysis Tests

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	DISEASE
P. DeP.	7- 2-48	5,360	+0.5	+0.8	+0.3	Acute febrile bronchitis
	7- 6	5,650	−6.0	−4.3	+2.3	
R. G.	7- 2	4,920	−0.5	−1.2	−0.7	Acute upper respiratory infection
	7- 6	5,300	−3.0	+1.0	−4.0	
J. Fan.	7- 6	9,220	0	−4.0	−4.0	Lung abscess
	7- 7	6,700	−1.0	0	−1.0	
A. P.	7-16	4,930	−5.7	−3.6	+2.1	Carcinoma of lung with secondary infection
	7-22	5,280	−2.5	−1.0	+1.5	
K. L.	7-22	7,390	−0.7	0	+0.7	Virus pneumonia
	7-28	11,400	−5.0	−5.0	0	
S. M.	9- 9	8,900	−1.0	+0.5	+1.5	Asthmatic bronchitis; bronchopneumonia
	9-10	9,850	−0.1	−0.3	−0.2	
R. B.	7- 8	6,550	−1.0	−5.5	−4.5	Prostatic obstruction; acute pyelonephritis
	7- 9	5,800	−2.5	−0.5	+2.0	
D. G.	7-26	5,680	−5.8	−2.7	+3.1	Acute myocardial infarction, fifth day
	7-28	6,330	−5.1	−4.8	+0.3	
J. F.	9-23	7,610	−0.5	0	+0.5	Chronic febrile bronchitis
	9-21	11,480	−0.5	+0.2	+0.7	
A. H.	9-21	3,820	+1.0	+1.2	−0.2	Virus pneumonia with asthma; recovering
	9-22	4,270	−1.0	−1.2	−0.2	
			Other Diseases; with Alarm Reaction			
			Negative Cytolysis Tests			
J. K.	7- 2	11,600	−12.0	−10.7	+1.3	Acute asthmatic bronchitis; status asthmaticus
	7- 8	9,650	−33.8	−34.0	−0.2	
A. B.	7-22	5,070	−16.3	−20.2	−3.9	Virus pneumonia, severe
	7-26	5,630	−2.6	+1.0	+1.6	
A. S.	9-10	36,900	0	−1.5	−1.5	Carcinomatosis; bronchopneumonia
	9-13	27,300	−21.7	−21.5	+0.2	
M. R.	9-10	11,020	−22.4	−21.2	+0.8	Fulmanent meningococcus meningitis
	9-11	9,910	−20.1	−21.5	−1.4	
	9-14					Died
L. R.	9-10	4,370	−3.4	−8.8	−5.4	Virus pneumonia, severe; migrating type
	9-13	5,120	−22.5	−21.6	−0.9	
	9-17	7,140	−0.4	+0.7	+1.1	
E. M.	7-16	14,500	−0.9	−1.0	−0.1	Staphylococcus osteomyelitis
	7-17	10,600	−7.0	−5.8	+0.2	
	7-20	12,500	−11.3	−10.7	+0.6	One day postoperative
	9-16	5,730	−2.9	−1.6	+1.3	Well
A. J.	9-16	6,010	−5.0	−4.5	+0.5	Pleurisy with effusion
	9-17	4,310	−1.2	−0.8	+0.4	

TABLE 5

Group V. *Normal Subjects*

	DATE	WBC PER CU. MM.	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECREMENT	PREVIOUS PPD SKIN TEST		COMMENT
						First	Second	
E. M.	3-11-47	4,520	−1.8	+0.3	−2.1	−	+	
J. B.	3-23-48	4,460	−3.5	−5.4	−1.9	−	+	
E. P.	2-15	5,080	−2.0	+2.0	+4.0	−	+	
	7- 1	4,520	+0.5	0	+0.5			
M. W.	6-30	4,980	0	−1.2	−1.2	−	−	
	7- 1	3,255	0	+3.1	+3.1			
S. J.	6-30	6,460	−0.2	+1.1	+1.3	−	−	
	7- 1	6,000	+1.3	−3.9	−4.2			
R. T.	6-30	6,180	+1.5	−0	+1.5	−	−	
	7- 1	5,870	−0.5	−0	+0.5			
G. M.	7- 7	3,770	−1.6	0	+1.6	−	±	
	7- 8	3,810	0	−1.3	−1.3			
M. Z.	7-15	3,610	−2.2	−0.7	+1.5	−	+	
	7-16	5,570	−1.5	−1.5	0			
LeC.	7-28	5,870	−3.1	−2.5	+0.6	−	+	
J. B.	9-28	5,740	−3.1	0	+3.1	−	+	
	9-29	4,340	−0.8	0	+0.8			
J. E.	10- 4	6,240	0	−2.0	−2.0	−	+	
	10- 7	5,590	−3.9	+1.0	+4.9			
C. B. F.	3-15	4,520	+2.5	+3.0	+0.5	−	+	
	6- 3	5,310	−3.6	−3.5	+0.1			
	6- 3							Second strength PPD placed
	6- 4							+++ local reaction
	6- 7	5,500	−1.5	−27.0	−25.5*			
	6- 9	3,410	−3.8	+1.1	−4.9*			
	9-13	4,020	−0.8	−0.3	−1.1			
J. M.	7-16	6,950	−0.6	0	+0.6	−	+	
	7-19	6,410	−0.6	−1.0	−0.4			
	7-19							First strength placed
	7-20							Second strength placed
	7-22	6,540	−1.0	−0.6	+0.4			++ reaction
	9- 9	8,900	−1.0	+0.5	+1.5			
J. V.	9- 8	3,360	−1.5	−0.6	+0.9	−	+	
	9-13	3,490	−0.4	−3.0	−2.6			First strength placed
	9-15							Second strength placed
	9-16							+++ reaction
	9-18	5,470	−2.5	−18.2	−15.7*			
	9-20	4,480	−1.2	−0.6	+0.6			
	10- 2	4,230	0	−2.1	−2.1			
B. W.	7- 9	5,470	−0.5	−1.0	−0.5	−	−	
	7-12	3,630	+0.7	−2.0	−2.7			
	11-10							First strength placed
	11-12					−		Second strength placed
	11-13	3,080	−2.5	−2.5	0			
	11-14							− negative reaction
M. U.	7- 9	4,770	0	−1.7	−1.7	−	−	
	7-12	4,600	+0.5	−1.4	−1.9			
	11-10							First strength placed
	11-12							− Second strength placed
	11-13	4,460	+0.7	+1.5	+0.8			
	11-14							− negative reaction

* Values not included in calculation of standard deviation of the mean.

Using the formula $\sigma = \frac{\epsilon(x^2)}{N}$ for the PPD increments on the above data, $2\sigma = 3.9$ blood may be lower than that for blood from sick patients. Twice the standard deviation of the mean of normals is 3.9.

psoas abscess which had been draining for two years (E. S.). None of these patients had more than a degree of fever and all maintained their weight and their feeling of well being. It will be seen that all the PPD decrements were below 10 per cent.

In table 3 (Group III) are listed patients with widely differing acute illnesses. The PPD decrements vary from 10 per cent in a man with a myocardial infarction (W. B.) to 54 per cent in a young house officer with agonizing renal colic (H. O'C.). Careful studies over many months have failed to reveal the presence of clinical tuberculosis in any of these persons. Four of the patients had PPD decrements below 10 per cent coincident with recovery (A.M., A.C., W.B., H. O'C.), and one showed no signs or symptoms other than extreme age (M. W.). All had positive intracutaneous reactions to first or second strength PPD (tested after cytolysis studies). The cause for these changes is obscure.

In table 4 (Group IV) are listed a series of duplicate studies on persons with a wide variety of acute illnesses. Some of these persons have had simple difficulties (P. DeP., R. G.); others have had dramatic illnesses (J. Fran., D. G.).

Some patients (Group IV) show an "autodestruction" of lymphocytes in whole blood. This may be an *in vitro* "alarm reaction" similar to the phenomenon induced in the intact host by the adrenocorticotrophic hormone (ACTH) of the pituitary gland (16, 17).

In table 5 (Group V) are given the values for PPD and saline control white blood counts on normal subjects with and without a positive cutaneous reaction to tuberculin. With the exception of the PPD decrements occuring within several days following a strongly positive cutaneous tuberculin reaction (C. B. F., J. V.), the values are low. When values not starred are subject to statistical analysis, twice the standard deviation of the mean is 3.8. It should be noted that this finding is for normal white blood cells existing under relatively ideal conditions for survival. The error of the method as applied to the effect of PPD on abnormal white blood cells may be as much as 5 per cent, as may be seen in Group I (table 1) in the day to day variations of a given patient whose clinical course is stationary (Ro.P., H. K.).

False positive reactions: The careful study of several patients who had PPD decrements of 14 to 25 per cent in their cytolysis test on repeated observations, and who were found to have no tuberculosis by clinical criteria, cultures, or by autopsy, led to the finding that the induction of a positive tuberculin skin test may be associated with an *in vitro* tuberculin cytolysis in the patient's blood when tested several days afterwards. This is also true in some healthy tuberculin-positive persons who normally have a negative tuberculin cytolysis test and yet show a transiently positive white cell test after administration of PPD intradermally (Group V, table 5).

Certain persons with acute febrile illnesses of a nontuberculous nature have shown a transient PPD decrement (Group III, table 3). This decrement has returned to zero upon recovery. Cultural and clinical evidence of tuberculosis has been absent in such patients both during the acute illness and subsequently. In several of these individuals an obvious bacterial infection has been present, for example a carbuncle, where a greater cytolysis to staphylococcus protein than

to PPD was observed. The majority of the miscellaneous acute illnesses studied (Group IV, table 4) have not shown this nonspecific effect. This type of false positive reaction is possibly an anamnestic effect of the acute infectious process upon subclinical tuberculosis

DISCUSSION

The observations reported in this paper indicate that few of the circulating white cells in homologous plasma of tuberculin positive "normal" people or of persons with chronic tuberculosis are affected by tuberculin. Even in highly active tuberculosis only a portion of the peripheral white cells are destroyed by tuberculin under the conditions of these experiments. By the same token, in none of the examples of highly active tuberculosis have we found a correlation between *in vitro* cytolysis and the size of the cutaneous tuberculin reaction. The earlier tissue culture type of experiment indicates that tuberculin causes greater white cell damage than we have observed and, if anything, the lymphocyte is the most frequent surviving cell type at the end of 24 hours. It should be remembered, however, that such experiments were conducted in static media free of homologous plasma, consisted of 24 to 48 hour observations on cell systems having a low survival of some cell types, especially the neutrophils, and were in no way quantitative estimates of cell populations. As one-half or more of the lymphocytes from peripheral blood survive the first hours of exposure to tuberculin *in vitro* as measured by the cytolysis test, and as lymphocytes are known to live up to three or four days in tissue culture, it is not surprising that discrepancies between the findings of cytolysis tests and tissue cultural methods exist.

The observation that a positive tuberculin test may be followed by a greater PPD decrement in the white cell lysis test sheds some light on the mechanism of activation of tuberculosis foci by an excessive injection of tuberculin, or the activation of a remote lesion by a local tuberculous process. In the same way, the presence of a positive tuberculin cytolysis test, as for example in persons with progressive tuberculosis, may indicate a recent liberation of tuberculin substances somewhere in the host. Likewise the reversion of the tuberculin cytolysis test to negative at the time clinical symptoms are ameliorated suggests that the local liberation of tuberculin has become minimal. It is of interest in this connection that we have observed the disappearance of the positive tuberculin cytolysis test coincident with clinical improvement in tuberculous pleurisy with effusion, and with the temperature fall after successful treatment of tuberculous pericarditis with streptomycin. The presence of an "anamnestic-like" tuberculin cytolysis test coincident with other acute disease suggests several interesting possibilities. For one thing, such undiagnosed febrile illnesses may be true active tuberculous infections which are promptly controlled by a relatively resistant host; or they may be inapparent minimal tuberculous "spreads" during intercurrent infections. Reactions of this sort also suggest a mechanism whereby one acute infection may activate a quiescent tuberculous focus of infection.

SUMMARY

1. A portion of the white blood cells in heparinized whole blood from patients acutely ill with tuberculosis is lysed by tuberculin (PPD) *in vitro* within one hour.

2. This phenomenon bears a rough correlation with focal allergic manifestations of the tuberculous process but not with the degree of the cutaneous reaction to tuberculin.

3. The mechanism of the tuberculin reaction is briefly discussed.

SUMARIO

Factores que Afectan la Citólisis in Vitro de los Leucocitos por la Tuberculina

1. Cierta porción de los leucocitos en la sangre íntegra heparinizada de los sujetos agudamente enfermos con tuberculosis es lisada por la tuberculina (PPD) *in vitro* en término de una hora.

2. Este fenómeno guarda una tosca correlación con las manifestaciones alérgicas focales del proceso tuberculoso, pero no con la intensidad de la cutirreacción a la tuberculina.

3. Discútese brevemente el mecanismo de la reacción tuberculínica.

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A SIMPLIFIED GUINEA PIG TEST FOR TUBERCULOSTATIC AGENTS[1]

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INTRODUCTION

The discovery of active chemotherapeutic agents in the field of tuberculosis has been made possible by testing them in experimentally infected animals. The need for tests requiring relatively small amounts of chemicals and short periods of testing has resulted in the development of new methods (see review by M. I. Smith (1)). Despite certain advantages of these, it seems that the classic guinea pig test is still indispensable in experimental tuberculosis work. With H. G. Wells and E. R. Long (1932), one "may feel quite sure that a drug which cures the disease in the guinea pig, or even influences it favorably, would more certainly be beneficial in the much less susceptible human being" (2). This view has been well confirmed by the success of the work initiated by Rich, Feldman and Hinshaw (3, 4) and others. As applied by these authors, however, the guinea pig test is applicable to the testing of only a few substances because of the need for large doses, long periods of testing, and large groups of animals.

An attempt has been made to simplify the guinea pig test without sacrificing its high degree of specificity. The results obtained during a four year period with a modification of the method are reported at this time, as others might wish to avail themselves of the test.

MATERIALS AND METHODS

Basic Principles of the Test

Preliminary studies of the experimental tuberculous infection of the guinea pig and its reaction to known tuberculostatic drugs, in particular 4,4′-diaminodiphenylsulfone, have formed the basis for the modification of the guinea pig test.

Like other investigators (5), we have learned that measurement of the degree of anatomical involvement is as good a criterion of tuberculostatic action as evaluation of the spread of the tubercle bacillus by culture methods. Survival tests with their requirements for large groups of animals, large quantities of chemicals, and long periods of experimentation, are reserved for substances which have proved their value in the test based on evaluation of anatomical involvement.

Study of the morphology of the primary focus in the experimental tuberculosis of the guinea pig reveals its tendency to spontaneous retrogression. This takes place, without any treatment, while the general disease progresses. This suggests the superiority of a test based on evaluation of a generalized infection. It would seem that the progress of the disease rather than the behavior of a primary focus

[1] From the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, and Summit Park Sanatorium, Pomona, New York.

or involvement of a single organ (omental test) should be used to evaluate tuberculostatic action.

Investigation of the tuberculostatic activity of 4,4′-diaminodiphenylsulfone has demonstrated the value of this substance as a standard for such activity in each single test. As this compound shows significant activity even after generalized infection has been already established, its use as a standard has helped shorten the period of testing. Furthermore, establishment of a standard of reference has made possible a well-defined tuberculostatic guinea pig unit. This unit is given by the minimal dose of any substance which has a tuberculostatic effect equal to that of the standard preparation of 4,4′-diaminodiphenylsulfone (50 mg. daily) under the conditions of the test. For the study of the relation between chemical constitution and tuberculostatic activity, the definition of such a unit would seem most useful.

In the scheme for evaluation of anatomical involvement, equal consideration has been given to the extension of the infection through the lymphatic system and to hematogenous spread. Inoculating dose, mode of inoculation, and the type of infecting organisms have been chosen in such a way as to ensure a progressive type of infection (50 per cent of the animals dead within eight to ten weeks) but one which may be significantly retarded by a tuberculostatic agent. Retardation, not cure of the disease, has been the aim in the development of this short routine guinea pig test, devised primarily for the screening of tuberculostatic agents.

Description of the Test

Experimental animals: Guinea pigs of either sex and of the approximate age of two months, weighing between 300 and 350 Gm. at the start of the experiment, have been found satisfactory. To make certain that the animals are in good condition for the test, they are kept in the animal house for several days prior to inoculation. Usually 100 animals are inoculated for one test and are divided into groups of ten.

Diet of experimental animals: The basis of the diet is formed by ground guinea pig pellets to which ascorbic acid 0.2 mg. per Gm. and ViDelta (1:10 dilution), containing 20 I.U. of Vitamin A per Gm. and Vitamin D 2.0 mg. per Gm., are added. Greens are added in the form of lettuce and spinach to the daily ration of 20 Gm. ground pellets.

Preparation of inoculum: In all experiments a strain of human tubercle bacilli (Summit Park #4313) has been used. This strain was isolated in 1942 from a patient suffering from far advanced pulmonary tuberculosis. In guinea pig tests for virulence, this strain was found to be the equal of strain H37Rv. The Summit Park strain has the morphological and cultural characteristics of *M. tuberculosis* var. human. and sensitizes guinea pigs to tuberculin. Both subcutaneous and intraperitoneal inoculation of various doses of this strain cause tuberculosis in the guinea pig of the classic Villemin type.

The strain has been cultured on egg media (whole egg 750 cc., egg yolk 150 cc., potato glycerin broth 600 cc., KH_2PO_4 10 per cent 15 cc., 2 per cent Malachite Green 18.75 cc.) and passed through guinea pigs twice a year. Third transplants from egg media between one and three months old have been used for preparation of the inoculum. The strength of the suspension in one-fifteenth molar Na_2HPO_4 is determined by counting the number of bacilli contained in .005 cc. of the fluid placed on a slide marked with a square centimeter. The suspension is diluted to a strength of 100,000 organisms per 0.1 cc.

Mode of inoculation: For inoculation the intraperitoneal route is used. It gives rise to a generalized infection faster than subcutaneous inoculation and allows exact measurement of the size of the primary lesion (omentum). The absence of fistulas, which commonly

develop after subcutaneous infection is desirable from the viewpoint of safety of the personnel handling the animals. The standard dose of inoculum has been fixed at 200,000 microorganisms. The inoculated animals are rotated in such a way that errors of dosing of the inoculum because of clumping in the syringe will be evenly distributed over the ten groups. Under the assumption that each group may have received an inoculum of different size, animals of each group of ten are distributed one each into ten new groups.

Drug administration: Drugs are administered either in the diet, orally through a syringe, or subcutaneously. When given in the diet, the drugs to be tested are given in the 20 Gm. of ground pellets described above. Feeding cups are constructed in such a way as to prevent excessive loss of the diet. The standard preparation of 50 mg. 4,4′-diaminodiphenylsulfone is contained in 10 Gm. of this diet and placed in the dish on top of 10 Gm. of the same diet free of the drug.

For testing at the level of the standard, a total amount of 10.5 Gm. of chemical is the minimum requirement. For comparison with streptomycin an amount of 4.2 Gm. of substance is needed.

Course of experiment: Drug treatment is started two weeks after inoculation and is continued for three weeks. The animals are weighed twice a week. They are sacrificed five weeks after inoculation.

Evaluation of anatomical findings: The anatomical findings are evaluated according to the following scheme.

Omentum:	
No tubercles grossly	negative
Tubercles present, weight below 1 Gm.	+
Tubercles present, weight between 1.0 and 2.0 Gm.	++
Tubercles present, weight between 2.1 and 3.0 Gm.	+++
Tubercles present, weight above 3.0 Gm.	++++
Spleen:	
No gross lesions visible	negative
Few gross lesions, visible with difficulty	+
Definite gross lesions	++
Numerous gross lesions	+++
Innumerable gross lesions	++++
Liver and lungs:	
Same as spleen.	
Cervical lymph nodes:	
No tubercles visible	negative
Few tubercles, limited to 1 node	+
Few tubercles in 2 nodes	++
Tubercles in 2 nodes with enlargement of node	+++
Tubercles in 2 nodes with very marked enlargement	++++
Mediastinal lymph nodes (include retrosternal, tracheobronchial, bronchomediastinal nodes):	
No tubercles grossly	negative
Tubercles present, weight below 0.6 Gm.	+
Tubercles present, weight between 0.7 and 1.2 Gm.	++
Tubercles present, weight between 1.3 and 1.8 Gm.	+++
Tubercles present, weight above 1.8 Gm.	++++
Abdominal lymph nodes (include gastric, portal, pancreatic, mesenteric, mesocolic): No tubercles grossly	negative
Tubercles present, weight below 0.8 Gm.	+
Tubercles present, weight between 0.9 and 1.6 Gm.	++
Tubercles present, weight between 1.7 and 2.4 Gm.	+++
Tubercles present, weight above 2.4 Gm.	++++
Retroperitoneal lymph nodes: Same as grading of mediastinal nodes.	

This scheme is easy to learn and has given identical results on the same material examined by two independent observers.

Calculation of tuberculous index: Every plus sign has the value of 25 per cent. The index of an individual animal is found by adding the indices of all eight organs mentioned in preceding paragraph. The group index is calculated by adding the individual indices and dividing the sum by the number of animals in the group (usually 10).

Recording of data: All data pertaining to the experiment are recorded on one sheet for each animal, including signs of toxic reactions and other clinical observations.

RESULTS

As already mentioned, the purpose of the test has been twofold: first, to screen chemicals for tuberculostatic action by comparing them with a standard at the same level; secondly, to establish the unit value as defined above to learn about the relation between chemical constitution and tuberculostatic activity. Most of the work has been concerned with screening, the results of which are the subject of separate publications. It might be mentioned here that the results agree well with those of other investigators using longer and more complicated tests. A more detailed study of some active compounds led to the establishment of their unit value (table 1).

TABLE 1

DRUG	MODE OF ADMINISTRATION	GUINEA PIG UNIT
		mg.
4,4′-diaminodiphenylsulfone	In the diet	50
Same	Subcutaneously	25
Streptomycinhydrochloride	Subcutaneously	20
4-aminophenyl-pyrazylsulfone	In the diet	100
4-aminophenyl-methylsulfone-hydrochloride	In the diet	200
Promin	In the diet	300

In evaluating the usefulness of this modification of the guinea pig test, an attempt was made to get a correct picture of its accuracy and of the significance to be attached to deviations from the control index. This index was found in 46 experiments to range from 46 to 67 per cent, the mean being 57 per cent. The standard deviation was 4.2, the variation coefficient 9.1 per cent, the standard error 0.62. In the same group of experiments the average index of the groups, treated with the standard, 4,4′-diaminodiphenylsulfone, was 37 per cent with a range from 26.5 to 47 per cent. The standard deviation was 7.9, the variation coefficient 17.2 per cent, the standard error 1.16. It seems of importance that the extremes of range given here were found at a time when the technical aspects of the test had not yet been perfected. Furthermore, a tendency of the control index towards one extreme is accompanied by the same tendency of the index of the standard group.

SUMMARY

Because of the necessity for a highly specific test for tuberculostatic agents which could be used with only small quantities of new chemicals, a modification

of the classic guinea pig test has been developed. Its execution, accuracy, and purpose have been discussed. The test requires five weeks for completion.

SUMARIO

Simplificada Prueba en el Cobayo para las Sustancias Tuberculoestáticas

Debido a la necesidad de contar con una prueba muy específica para las sustancias tuberculoestáticas, que pueda usarse con pepueñas cantidades de nuevos productos químicos, se ha elaborado una modificación de la clásica prueba en el cobayo. Discútense aquí la ejecución, exactitud y propósito de la misma. La prueba requiere cinco semanas para completarla.

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AN EVALUATION OF A METHOD OF OBTAINING GASTRIC WASHINGS[1,2]

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INTRODUCTION

Examination, culture, and animal inoculation of the gastric contents of patients suspected of having pulmonary tuberculosis has long been an accepted useful adjunct for the establishment of a positive bacteriological diagnosis. Meunier (1) first used this method in 1898 upon children because of their habit of swallowing their sputum. It was not until 1927, however, that Armand-Debille (2) demonstrated that gastric washings were of value in positively establishing the diagnosis of pulmonary tuberculosis in adults whose sputum had been repeatedly negative for tubercle bacilli.

Roper and Ordway (3) in 1941 demonstrated: (*1*) that the results of a single gastric lavage were insufficient to establish the diagnosis; (*2*) that usually a series done on consecutive days was necessary; and (*3*) that an increment in the number of lavages brought an appreciable rise in the percentage of positive results.

Studies made to determine the relative value of culture methods and animal inoculation have proved that all available methods of study should be applied in the search for *M. tuberculosis*. An exception may be made for the direct examination of a smear of gastric washings. In particular, Kayne and Hounslow (4), Roper and Ordway (3), Sasano and associates (5), Robinson and Dunn (6), have shown that simultaneous inoculation of animals and culture media are needed to obtain the highest percentage of positive results, as frequently one will be positive and the other negative. They have pointed out the inaccuracy of direct examination of the gastric smear, how seldom it is positive, and often falsely so. Indeed, Roper and Ordway (3) obtained only 41 smears positive for acid-fast bacilli from 983 patients, 660 of whom had roentgenographic evidence of presumably active tuberculosis. Kayne and Hounslow (4) found that false positive results occurred on direct examination of smears because of contamination of tubes and glassware with acid-fast saprophytes. In addition, there is always the possibility that acid-fast bacilli such as the butter bacillus and Timothy hay bacillus may be in the stomach.

Other experiments have indicated the possible effects of the gastric environment upon the tubercle bacillus. A considerable portion of the bacteriologic diagnosis of tuberculosis in this country is performed in federal and state-financed

[1] From Veterans Administration Hospital 48 and the Communicable Disease Center, U. S. Public Health Service, Atlanta, Georgia.

[2] Published with the permission of the Chief Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

laboratories, which receive specimens for study that in some cases may be many hours or even days old. As a consequence, the effects of the gastric secretions on the tubercle bacillus over a prolonged period are important.

Piasecka, Zeyland, and Zeyland (7) of Poland indicated in their work that the saliva of some patients had a marked inhibitory effect upon the tubercle bacillus in culture. Roper and Ordway (3) exposed the tubercle bacillus to normal hydrochloric acid for four days without apparent effect. They also found that free hydrochloric acid in the specimen did not harm the bacillus and that bile had no effect upon it. Floyd and Page (8), however, showed that prolonged exposure to gastric juice itself had an adverse effect upon the cultures of *M. tuberculosis*. In addition, they discovered that duodenal secretion had no such effect. Almost all workers have suggested that the various digestive enzymes may have an injurious effect upon the tubercle bacillus. Moreover, as these enzymes probably require a prescribed hydrogen ion concentration in which to act, the acidity of the stomach has an indirect, but nevertheless potent, effect upon the viability of the bacillus. In a study made to determine the effect of the time element, Sprick and Towey (9) found that a delay of more than 24 hours reduced the percentage of their positive results. Using both animal inoculation and culture methods, they made a 73 per cent positive diagnosis for tubercle bacilli on gastric specimens treated and cultured immediately upon obtaining them from the patient. After a delay of 24 hours, they had only 45 per cent positive findings. With a delay of 48 hours, a positive diagnosis was made in only 21 per cent of the specimens. Their specimens were treated with an equal volume of 4 per cent sodium hydroxide and 0.2 per cent alum immediately, and at 24 and 48 hour intervals, respectively.

Gastric lavage in this hospital is done for two reasons: to establish a positive diagnosis of pulmonary tuberculosis in patients with the typical picture of tuberculosis on chest films; and to evaluate the progress of the patients' disease. This study was undertaken to determine the effect of certain variable factors upon our results; and to study the efficiency of various sized tubes for removal of the gastric contents from the stomach. It is the practice of some European laboratories to use a number 30 French gastric tube, which might be more effective in obtaining the tubercle bacilli from the stomach. The United States Public Health Service Tuberculosis Evaluation Laboratory carried out the culture and animal inoculation work on our first 53 patients. The rationale of the large gastric tube is based on the assumption that the tubercle bacilli are held in the thick mucous secretions of the stomach and that they are also deeply embedded in the rugal folds. The small Levine tube with suction applied does not dislodge these bacilli. With the large tube a large volume of sterile water is introduced rapidly into the stomach with some force. The rugae are washed clean by the force of injection and, when the water is siphoned out, the bore of the tube is large enough to admit large masses of the mucinous material with ease. In addition, it was felt that the introduction of such a large portion of water would dilute the gastric juice to such an extent that the factors which reduce the

viability of the bacilli might be inhibited, whether they be acid, enzyme, or other factors.

TECHNIQUE

The first study consisted of a comparison of the efficiency of the large and the smaller calibre tubes. Each of the first 53 patients, all having repeated negative sputum examinations for tubercle bacilli, had four lavages on successive mornings. The large and small tubes were alternated each day and the lavage was done early in the morning so that often the patients were awakened from sleep for the procedure. The stomach was therefore in a fasting state. Simultaneous 24 hour concentrated sputum specimens were examined during this four day period. In each instance 250 to 300 cc. of distilled water were poured down the large tube or injected through the Levine tube with a 30 cc. syringe. When utilizing the large calibre tube, the contents were immediately siphoned into a large sterile basin, or not infrequently were vomited by the patient into the basin. Usually 250 to 500 cc. of material were obtained. With the use of the small tube, suction was applied at the end of each injection and a smaller total volume, usually 50 to 100 cc., was obtained. It should be made clear that some patients had two or three of these series over a period of months and that four gastric lavages are not regarded as a sufficient number if all studies are negative for tubercle bacilli.

In order to reduce the chances of false positive results, the tubes, syringes, containers, and basins were daily cleaned with soap and water, washed with sodium bicarbonate to dissolve any mucus present, washed with soap and water again, rinsed thoroughly with distilled water, and autoclaved. When the study was begun, it was felt that all patients would prefer the Levine tube because of the smaller size and ease of passage via the nasal route. It was surprising to find that about 55 per cent of the patients preferred the large 30 French gastric tube passed by mouth. It can be passed rapidly with only one cooperative swallow on the part of the patient to get it past the larynx. This procedure is more rapid than with the small tube, but less tidy as the subject not infrequently vomits. One factor became apparent as to the patient's choice of tube. He preferred the tube he did not take first. The first day's experience was more traumatic mentally and physically. Since the first sight of the large tube was so terrifying, most patients "learned" on the small tube and therefore preferred the larger calibre which they received after being "trained."

Once collected, the specimens were treated in the following manner: The specimen was placed in a refrigerator until sediment formed. The supernatant fluid was poured off and the sediment was centrifuged for 15 minutes. Smears were made. If the specimen was thick and mucoid, 10 cc. of sodium hydroxide were added; if it was thin, 2 cc. of 6 per cent sulfuric acid were added. If sodium hydroxide was used, an inverted rubber stopper was inserted and the specimen was incubated for 20 minutes at 37°C. It was shaken every 5 minutes. The specimen was centrifuged again and the supernatant fluid poured off. If the specimen was treated with sodium hydroxide, two drops of hydrochloric acid were added and it was cultured on four tubes of Jensen's modification of Lowenstein's medium (10). If the specimen was treated with acid (2 cc. 6 per cent sulphuric acid), it was left for 10 minutes at room temperature, during which time it was shaken vigorously. Then 10 cc. of re-distilled water were added and it was centrifuged as above. The supernatant fluid was poured off and the sediment inoculated directly onto four tubes of the medium. Cultures were kept for 8 weeks at 37°C. before being discarded as negative. Young guinea pigs which were injected with 1.0 cc. of the homogenized neutralized specimen inoculated subcutaneously into the groin were autopsied at the end of 6 weeks.

In addition, the specimens from 30 of the 53 patients were divided equally into three parts: one treated and cultured within 4 hours, the others at 24 and 48 hours, respectively. It was believed that in this manner some relationship between the delay and dilution factors might become apparent. It was realized that some inherent error could be present, for Roper and Ordway (3) have shown that, when gastric specimens are divided, some parts are negative while other parts of the same specimens are positive for tubercle bacilli.

RESULTS

Direct Examination of Smears

A careful study was made of the smears from the specimens, a minimum of 30 minutes being spent on the examination of each smear. Of 206 gastric washings from the 53 patients, only 17 smears (14 patients) positive for acid-fast bacilli were obtained. In 6 of the 14 patients, culture and guinea pig inoculation with that particular washing were negative for tubercle bacilli, although 4 of the 6 were found to have positive cultures on a subsequent examination. Therefore, from 206 gastric washings, the presence of acid-fast bacilli on direct examination of the smear was of value in only 2 cases. It is believed that this percentage is too low for the amount of work involved, especially when compared to the possible errors inherent in the direct examination of smears. For example, there was considerable doubt as to the diagnosis of active tuberculosis in these 2 patients with "positive" smears. One was a white man 20 years of age who had had a tuberculous pleural effusion one year previously proved by animal inoculation. Repeated roentgenographic examination of the chest made during the time of this study showed no evidence of activity. Twelve gastric cultures, three guinea pig inoculations and many sputum examinations were negative for tubercle bacilli. The second case was a 23 year old white man who has never had demonstrable tubercle bacilli in the sputum, although he had a cavity which had closed before admission to this hospital. Cultures of 12 gastric washings, a bronchial washing, and many sputum specimens have all been negative for *M. tuberculosis* or fungi. Repeated animal inoculation of similar specimens has also been negative. These patients have been sent to the Veterans Administration Rehabilitation Center as apparently arrested.

In order to examine the possibility of "false positive" smears, each of 12 hospital workers with negative chest roentgenograms were subjected to two gastric lavages. One individual had smears positive for acid-fast bacilli on both occasions, and a specimen from a second individual contained a single suspicious bacillus. Unfortunately, cultures and animal inoculation were not done upon the 2 positive specimens, but a thorough study, including monthly roentgeongrams and gastric lavages with proper culture and guinea pig inoculations, have failed to reveal signs of tuberculosis. In the remaining 11 cases, culture and guinea pig inoculation revealed no tubercle bacilli. The possibility of "false positive" smears did not seem remote after this experience.

Cultures

In table 1 may be seen that, from the 206 specimens, positive cultures were obtained in 29, or 14 per cent.

Of the 29 positive cultures, 15 were from specimens taken with the large tube, and 14 with the small tube. The number of colonies in each culture was recorded and no conclusions could be drawn in regard to the effectiveness of either tube in relation to the number of colonies per culture. In table 2 the efficiency of the gastric culture in 53 cases is compared with the sputum

examination by the direct smear method. The results are correlated with the stage of the disease as determined by roentgenographic means.

In each series of four gastric lavages only one guinea pig was used. The guinea pig was injected with the first day's specimen only on the day it was obtained. In 6 cases the guinea pigs yielded positive findings where the cultures were negative. In 3, however, cultures on a subsequent day were positive. In the remaining 3 cases, 16 negative cultures and one positive animal inoculation were obtained from four specimens.

There were 9 patients whose specimens were positive for tubercle bacilli on culture although negative on guinea pig inoculation. It should be pointed out,

TABLE 1

Percentage of Gastric Cultures Positive for M. tuberculosis Based on 206 Specimens

	TOTAL NUMBER	PER CENT POSITIVE	NUMBER POSITIVE		TOTAL
			Large tube	Small tube	
Specimens	206	14	15	14	29
Patients	53	30	16		16

TABLE 2

Number of Patients with Gastric Culture Positive for M. tuberculosis Correlated with Roentgenographic Stage of Disease and Subsequent "Positive" Sputum

	POSITIVE GASTRIC CULTURE; NEGATIVE SPUTUM SMEAR	POSITIVE GASTRIC CULTURE; POSITIVE SPUTUM SMEAR	NEGATIVE GASTRIC CULTURE; POSITIVE SPUTUM SMEAR	NEGATIVE GASTRIC CULTURE; NEGATIVE SPUTUM SMEAR
Minimal	7	5	4	12
Moderate	2	6	0	3
Far advanced	4	6	1	0
Total	13	17	5	15
Cavitation	5	10	1	1

however, that more specimens were cultured than were tested by animal inoculation.

Twenty-two of the 53 patients finally were found to have sputum positive for tubercle bacilli. It is interesting to note that in 11 the bacteriologic diagnosis was established for the first time during the 4 days of gastric washings. Whether or not the tubes cause severe enough coughing to bring up "positive sputum" for the first time is purely conjectural. Most patients found that the large tube caused an irritated throat or pharynx. Two of the "postive" sputum specimens came the day following the bronchoscopy.

A classification of the patients according to the roentgenographic findings

revealed that 11 had far advanced tuberculosis. A positive bacterial diagnosis was made on all of these cases. There were 11 patients whose disease was classified as moderately advanced and of these a positive bacteriologic diagnosis was established in 7. The other 4 had all discharged sputum positive for tubercle bacilli in the past. They were near the end of a long hospital stay and have since been rehabilitated. Of the 28 minimal cases, 13, or 46.4 per cent, were proved positive for *M. tuberculosis* is by cultures and guinea pig from gastric washings or by additional sputum studies. Of the 15 patients found to be noninfectious by a series of four gastric washings, only 6 failed to have additional gastric studies. In fact, most had from twelve to fifteen gastric lavages. The 6 patients who received only four washings had stable minimal lesions of many months' duration and had come to this hospital for a periodic review which occupied only a few days. Of the 53 patients, 17 were found to have cavitation, and in 16 a positive bacteriologic diagnosis was established. The one exception was an elderly man with bullous emphysema and no typical inflammatory cavitation. Three of the 53 patients were proved to our satisfaction to have no disease; 2 had an atypical history and negative roentgenographic and bacteriologic studies. The third died of silicosis and postmortem revealed no tuberculosis.

Specimens from 30 patients were divided into 3 portions, one of which was prepared immediately and cultured; the other portions were kept 24 and 48 hours respectively before being cultured. Of these 120 cultures, 11 were positive from those prepared immediately; 6 were positive of those kept 24 hours, and 5 were positive of those kept 48 hours. This series is too small in itself to do more than indicate a trend, but the results were in agreement with the previously quoted observations of Sprick and Towey (9).

Unfortunately, due to shifting personnel, the United States Public Health Service was unable to continue with this program. Our own laboratory was likewise shorthanded, and the second 50 patients of necessity were treated in a different manner. These 50 patients each had a series of four consecutive gastric washings, which were treated and prepared for culture immediately as outlined above, but each specimen was kept and combined on the fourth day into one and inoculated upon four tubes of culture medium and into one guinea pig. Necessarily part of each specimen was four days old on inoculation, although they were treated on the day of collection and kept in the ice box. From these 50 patients, 13 specimens were positive for tubercle bacilli on culture or animal inoculation. This represents 26 per cent positive results in contrast to 35.8 per cent positive specimens obtained from the previous 53 patients. Thus, the first method achieved 9.8 per cent more positive results than the second method. In addition to the time element, however, the first method included the use of 16 tubes of culture medium to each patient, in contrast to four for the second method.

SUMMARY

Fifty-three consecutive patients whose sputum had been previously negative for tubercle bacilli were subjected to repeated gastric washings, the contents of

their stomachs were collected and studied in various ways in an attempt to find the best method for collection and culture of gastric contents. Studies of the sputum were continued during these tests. An additional group of 50 patients with sputum negative for tubercle bacilli were treated by an abbreviated culture technique and 9.8 per cent fewer positive results were obtained.

CONCLUSIONS

1. The size of the tube used in collecting the specimen is of no consequence.
2. The length of time between the collection and the culture of the specimen is of considerable importance. The shorter the time, the greater the chance of success.
3. Smears made of the gastric contents are unreliable whether found to be positive or negative for acid-fast bacilli.
4. A greater number of positive cases will be found if repeated gastric washings are done.
5. Cultures should be made of each gastric lavage immediately and the concentrates of several should not be combined as one.
6. Both guinea pig inoculation and cultures should be used in the search for the tubercle bacillus in gastric washings.

SUMARIO

Valuación de un Método para Obtener Lavados Gástricos

En 53 enfermos consecutivos cuyo esputo había sido previamente negativo para bacilos tuberculosos, verificáronse lavados gástricos respetidos. Recogióse y estudióse en varias formas el contenido del estómago de los mismos tratando de descubrir la mejor técnica para la colecta y cultivo del contenido gástrico, continuando los estudios del esputo durante dichas pruebas. En otro grupo de 50 enfermos de esputo negativo para bacilos tuberculosos se empleó una técnica cultural abreviada, obteniéndose un 9.8 por ciento menos de resultados positivos.

CONCLUSIONES

1. El tamaño del tubo empleado para recoger el ejemplar no tiene importancia.
2. El tiempo transcurrido entre la colecta y el cultivo del ejemplar reviste considerable importancia. Mientras más breve ese tiempo, mayores son las probabilidades de éxito.
3. Los frotes preparados del contenido gástrico son poco fidedignos, ya resulten positivos o negativos para bacilos ácidorresistentes.
4. El número de casos positivos será mayor si se ejecutan lavados gástricos repetidos.
5. Deben hacerse inmediatamente cultivos de cada lavado gástrico, sin combinar en uno solo los concentrados de varios.
6. En la busca del bacilo tuberculoso en los lavados gástricos deben emplearse tanto la inoculación en el cobayo como los cultivos.

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Case Reports

PATHOLOGICAL AND EXPERIMENTAL STUDIES OF BOECK'S SARCOID[1]

1. Report of a Case with Panarteritis, Periarteritis, Terminal-hypertension and Uremia, and the Reproduction of a Sarcoid-like Lesion in Guinea Pigs

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INTRODUCTION

This is the first of a group of reports that will enlarge upon the thesis of the intimate relationship between sarcoidosis and tuberculosis. Included in these studies is the case report of a patient who was consistently anergic to first and second strength of PPD and was unique in several respects. There was specific involvement of the vessels generally, plus a nonspecific necrotizing arteritis and periarteritis associated with hypertension, uremia, and death. Emulsions of the lymph nodes were negative for tubercle bacilli by smear, culture, and microscopic section. When this material was injected into guinea pigs, however, sarcoid-like lesions were produced in which numerous acid-fast bacilli were found. The microorganisms failed to grow on culturing. The animals responded to tuberculin.

The second report deals with the isolation of banal organisms from autopsy and surgical sarcoid material which had a bactericidal action on tubercle bacilli.

The third report is on a theory of the pathogenesis of sarcoidosis as deducted from further experimental studies in animals and BCG vaccination in two human cases of sarcoidosis.

CASE REPORT[2]

A colored male, age 22, had been ill for approximately two years. His symptoms began with nosebleeds and headaches, the latter becoming severe. In the first year he lost 30 pounds in weight. What brought him to the hospital eight months before death was chest pain in the right side and a nonproductive cough. He had had paroxysms of fever, chilliness, and night-sweats. On admission he looked chronically and acutely ill. His conjunctivae were injected and there was marked enlargement of both lacrimal and, to a great extent, the parotid glands. Small soft lymph nodes were noted in anterior and posterior cervical, occipital, and inguinal regions. Both epididymi were enlarged, nodular, and indurated. Many rales were heard throughout the chest. Examination of the ocular fundi showed that the retinal vessels were normal but in the region of the superior nasal vein at the left of the disc there was a linear exudate. A flame-shaped hemorrhage was present in the region of the inferior nasal vein four diopters below the disc. There was general haziness of the cornea and the entire pupillary body of the left eye was drawn in an irregular fashion to the lens capsule. A roentgenogram of the chest showed ill-defined shadows of increased density scattered throughout the lower two-thirds of both lung fields, more marked on the right side. The hilar shadows were considerably enlarged bilaterally. The Mantoux tests with first and second strength PPD were negative as were culture and animal studies of the sputum for tubercle bacilli. Biopsies of three lymph nodes yielded tissue which presented the typical findings of sarcoidosis. Of special interest was the invasion of specific granulomatous

[1] From Institution for Tuberculosis Research and the Research Foundation of the University of Illinois College of Medicine and the Bruns General Hospital.

[2] Condensed from a summary by Dr. Eric Hausner.

tissue into a medium-sized blood vessel with thrombus-like occlusion of the lumen. The blood count was not remarkable; the total proteins were 6.5 Gm. per 100 cc. with an A.G. ratio of 1.6. Examination of the urine revealed no abnormalities. Roentgenograms of the hands and feet were normal.

CLINICAL COURSE AND SUBSEQUENT LABORATORY FINDINGS

The general course was gradually downhill. One month after admission a generalized rash developed, manifested by pinpoint to millet seed-sized, dry, scaly papules corresponding to the sites of hair follicles. The microscopic findings in these papules were compatible with sarcoidosis. These lesions regressed and were not present six months later. The lesions of the epididymi likewise disappeared before those of the skin. Seven months after admission, or one month before death, the patient became confused and would respond only with difficulty. His vision decreased markedly. Multiple irregular masses were palpable in the abdomen. His temperature became slightly elevated and he died twenty-two months after the onset of his complaints. *Tuberculin tests:* On numerous occasions including the last month of the disease the tuberculin tests were persistently negative to the first and second strength of PPD. *Urine:* Four months before his death the urine was normal. Albuminuria with minimal cylindruria and an occasional leukocyte or erythrocyte then appeared. These abnormalities increased to a marked degree. The specific gravity was recorded as being low. *Blood:* A.G. ratio remained normal until four months before death, when the serum proteins were 7.1 mg. per 100 ml. (albumin 2.9, globulin 4.2, A.G. ratio 0.69). Three months later the readings were: total proteins 7.2, albumin 3.6, globulin 3.6, and an A.G. ratio of 1. Retention of nitrogenous products began one month before death, when the readings were nonprotein nitrogen 68, urea nitrogen 54, creatinine 3.9 mg. per 100 cc. The carbon dioxide combining power was 22.1 volume per 100 cc. and the concentration of chlorides was 429 per 100 cc. The erythrocyte sedimentation rate varied from 100 to 150 mm. per hour. The hemoglobin concentration dropped to 13 Gm. The erythrocyte count was 4,300,000, and the total leukocyte count was 8,350 cells per cu. mm. with a normal differential. *Blood pressure:* On admission, the blood pressure was not remarkable but rose to 160 systolic and 130 diastolic in mm. of mercury two months before death. The electrocardiograms were normal except for the presence of a sinus tachycardia. *Roentgenograms:* Repeated films of the chest up until one month of death showed small increased densities which showed evidences of some regression and finally stabilized. *Abdomen:* Flat plates of the abdomen and roentgenographic studies after barium meals were repeatedly negative. Roentgenographic examination of the hands and feet revealed no abnormal findings until three months before death when evidence of periosteal thickening and demineralization was described. One month before death the changes seemed to be less than previously but the proximal one-third of the first metatarsal was definitely involved in the manner described above.

The vitreous of both eyes, but especially of the right, developed many opacities. The final diagnosis was Boeck's sarcoidosis involving the kidneys, lungs, eyes, skin, epididymi, and possibly the small intestine.

POSTMORTEM FINDINGS

The body was emaciated, measuring 69 inches in length and weighing 95 pounds. The only significant external findings were small "shot-like" lymph nodes in the axilla and in the inguinal regions. Small atrophic scars were found over the skin of the arms and legs. There were a few dense fibrous adhesions between the wall of the pleural cavity and the lateral aspect of the right lung.

Lungs: The total weight of the lungs was 1,000 Gm. There were scattered fibrous and fibrinous exudate over both lungs. Beneath the pleura were pinhead to 6 mm. nodules. On palpation, larger nodules were noted as well as fluctuating areas, especially in the upper lobes. The lower lobes contained irregular areas of consolidation. On sectioning, the nodules were gray to black to yellow and granular; or they were composed of small to large thin-

walled cavities up to 2 cm. in diameter. In some instances normal lung parenchyma surrounded the nodules, while in others wide zones of red to gray granular areas of consolidation were present. This was especially true in the lower lobes. Some of these cavities extended directly into dilated bronchi.

Lymph nodes: The hilus, peritracheal, peribronchial, and periaortic nodes were enlarged up to 3 by 2 by 1 cm. and on section were mottled gray black. In some of the nodes the cortex was grayish pink and homogeneous with an occasional yellow fleck. The heart weighed 275 Gm. and small 3 mm. verrucae were present on the free border of the mitral valve, 2

FIG. 1. (upper) Both kidneys cut open. Note gray nodular and wedge-shaped lesions that involve cortex and medulla. The right kidney is less involved than the left.

FIG. 2. (lower) Left kidney. Note nodular masses that disfigure the organ.

mm. above the corona. The liver weighed 1,200 Gm. and its surface was smooth although studded throughout with miliary nodules which were pinhead-sized and grayish white. The sectioned surface was reddish brown with exaggerated markings. The small nodules described beneath the capsule of the liver were present throughout the parenchyma.

The kidneys weighed 250 Gm. together (figure 1). The surfaces, especially of the left (figure 2), were deformed by large, tan nodules which extended above the surface and measured up to 4 cm. in diameter. The capsule stripped with some difficulty leaving an irregular surface with the nodules already described. In the center of some of these nodules were irregular areas of light yellow. The nodules described on the surface extended throughout

the entire parenchyma and measured up to 2.5 cm. in width and 1.5 in depth; in some instances they were wedge-shaped. The architecture of the parenchyma was otherwise discernible although there was diffuse purple yellow and red mottling. The pelvis was not dilated and the mucosa was pale. The peripelvic fat was serous in nature. The prostate and seminal vesicles were essentially normal. The testicles together weighed 30 Gm. The epididymi were diffusely indurated and slightly nodular. On section they appeared to be transformed into dense fibrous connective tissue in which small islands of a lighter tan were noted. There was no evidence of caseation or granuloma on gross examination. The tunica vaginalis and tunica albuginea appeared markedly thickened. The testicle proper was discolored a yellow tan in which numerous fibrous strands were noted. The seminiferous tubules did not separate easily.

Brain and cervical cord: Except for some edema, the piaarachnoid was grossly not remarkable. Both eyes were removed and sent to the Army Medical Museum. The report will appear in another publication.

HISTOPATHOLOGY

Lungs: Scattered throughout the section were discrete nodules composed of epithelioid cells and occasional multinucleated giant cells. There was no reaction about these nodules. The cavities described in the central portions of the pneumonic areas were lined by dense fibrous connective tissue although it was very narrow in places. At such points dilated vessels as well as alveoli encroached very close to the lumen. In the smaller cavities, bronchial epithelium, high columnar in character, for the most part denuded, were noted. In some areas of the wall there were broad zones, easily occupying an entire low power field in which only hyalinized connective tissue was found with an occasional large giant cell of the foreign body type, swollen histiocytes, and round cells. There was also a proliferation of bronchial epithelium to form pseudoadenomatous areas. Occasionally such a structure was filled with fibrin and pus cells. Broad bands of fibrous connective tissue were found throughout the section in which an occasional epithelioid cell and giant cell could be found. The intervening lung parenchyma was composed of alveoli which were packed with pus cells and fibrin. One could still discern dilated atria and alveoli suggestive of an emphysema. The pleura was markedly thickened and was fused with some of the focal areas of fibrous connective tissue of the lung parenchyma. Here, too, one found a giant cell of the Toulon or even the Langhans' type in addition to the foreign body variety. Elastica Van Gieson stain revealed that the hyalinized fibrous connective tissue was dispersed through the lung parenchyma as focal nodules as well as connecting bands, all staining red to reddish pink. The walls of the cavities were lined by dense fibrous connective tissue for only approximately one-third of their diameters, the remainder being composed of delicate fibrils staining reddish pink. A striking feature was the paucity of elastic fibrils in the alveolar walls. One noted small fragments of black staining fibrils on only one aspect of an alveolar wall or none at all. The dilated bronchi with intact epithelium described contained only an occasional elastic fibril. Many of the veins presented a thickening of the internal elastic membrane with proliferation of fibrils as well as interruption of the internal elastic membrane. In some the intima was wide as a result of connective tissue proliferation.

Hilus and peritracheal lymph nodes: Despite the fact that 90 per cent of the lymph node was involved in the granulomatous process, the marginal sinuses were wide and showed practically no involvement. The normal architecture of the node had been entirely disrupted. Both cortex and medulla were the seat of fibrosis and hyalinization in which an occasional giant cell and groups of epithelioid cells were found. Occasionally there were typical granulomas composed of an epithelioidfibrocyte type of cell as well as an occasional giant cell. Silver stain revealed an intricate network of argentophil fibrils extending throughout the entire gland showing only rare dissolution within some of the active granulomas. Some of the giant cells presented inclusions composed of irregular deep blue staining bodies (hematoxylin and eosin stain), the so-called Schaumann inclusion bodies. Other giant cells contained vacuoles or phagocytized nuclear debris. On examination of five left axillary

nodes, the involvement could be traced from a single healed nodule in the center of a follicle up to 50 per cent involvement of the node. In every case the specific granulomas were found in the center of the follicle and never in the marginal sinuses. Stages were noted from the epithelioid tubercle through those with fibrinoid central necrosis and finally to those showing hyalinized scarring. Silver stain revealed only slight dissolution of the argentophil fibrils, especially in the region of specific granulomas. Crystal violet stain was negative for amyloid.

There was no specific involvement of the heart, spleen, pancreas, or gastro-intestinal tract.

Liver: Scattered throughout the liver were miliary nodules composed mainly of a coagulation necrotic material in which nuclear debris was still in evidence with a small peripheral zone of fibrocytes, occasional giant cells, and a zone of lymphocytes. The liver cords otherwise were fairly well preserved. The capillary sinuses were wide and there was an increase in periportal connective tissue. Sudan II stain revealed a diffuse deposit of lipoid material in the liver cells as well as in the central portion of the tubercles described.

Kidneys: The larger nodules described grossly were composed of coagulation necrotic mazerial in which ghosts of the original structure were still discernible. This was even more clearly demonstrated by the Elastica Van Gieson stain. There were no specific or round cell infiltrations about the necrotic zone but capillary dilation was prominent. The necrotic foci blended in with the kidney parenchyma although there was a marked interstitial fibrosis adjoining the nodules. In addition to these large areas, there were smaller foci composed of epithelioid cells which sometimes showed central fibrinoid necrosis and contained a rare giant cell. In other places such nodules were composed of hyalinized connective tissue only. A striking feature was the involvement of the medium-sized and smaller arteries. The medium-sized arteries, especially in the medulla, were surrounded by and invaded with a granulation tissue that was composed of fibrous connective tissue for the main part, histiocytes, and an occasional epithelioid and giant cell. Many of the vessels were almost completely occluded by such well-organized thrombi. Sections of the wall of the artery were entirely replaced by a similar pathology which interrupted the elastic and muscle tissue bundles. Many of the small arteries of the cortex were surrounded by epithelioid cells, giant cells, and a few round cells; media and adventitia were anuclear while the intima still maintained an intact endothelium (figure 3). Other vessel walls were entirely anuclear as well as the surrounding tissue for distances of three and four times the width of the vessels (figure 4). There was no cellular reaction of any kind. The walls were edematous and stained diffusely pale pink with hematoxylin and eosin. Still other medium-sized vessels were completely obliterated by dense fibrous connective tissue in which recanalization was present or absent. Elastica Van Gieson stain revealed in such instances an interruption of the internal elastic membranes with marked proliferative changes in the intima to complete occlusion (figure 5). Other changes consisted of dilatation and atrophy of the convoluted tubules in which numerous casts were noted. There was marked interstitial fibrosis and a certain amount of thickening of the afferent arterioles to the glomeruli. Some of the glomeruli showed atrophy and hyalinization of the glomerulus proper. The medulla was relatively uninvolved. The pelvis showed a slight amount of round cell infiltration beneath the epithelium but this was not excessive. Fat stain revealed that the central portion of some of the large necrotic areas contained much fat and that numerous phagocytes also laden with fat surrounded such areas, a fact not clearly evident with the hematoxylin and eosin stain. There also appeared to be fat in the glomerular capillaries, being present in the lumen of some of these vessels as well as in the endothelium. Many of the casts took the fat stain. The epithelium of the tubuli showed very little fat.

No definite abnormalities were noted in the prostate. In the epididymi there was an increase in fibrous connective tissue which in places effaced some of the ducts. In addition, there were accumulations of round cells in which swollen epithelioid cells were noted. Although these infiltrations were not characteristic of a specific involvement, they were very suggestive of transformed specific nodules by secondary round cell infiltration.

Testicle: The tunica vaginalis was markedly thickened by dense fibrous connective tissue in which small granulomas were scattered, composed of epithelioid cells and round cells. An occasional giant cell was noted. The vessels showed no specific involvement. There was a marked increase in fibrous connective tissue within the testicle proper with reduction of the number of interstitial cells. Spermatogenesis was not noted and there were no spermatozoa in the lumina of the tubules.

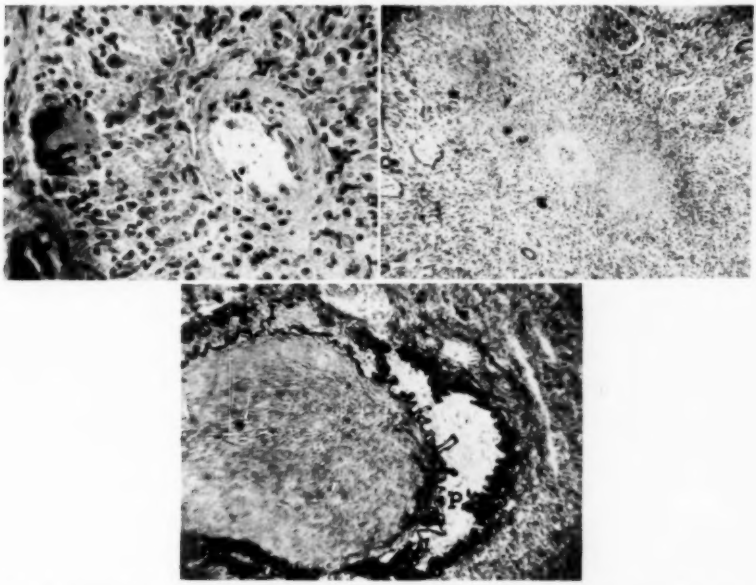

FIG. 3. (upper left) Specific granulomatous periarteritis and arteritis of small artery of kidney. Note typical sarcoid granuloma about vessel and edematous vessel wall with some cellular infiltration.

FIG. 4. (upper right) Nonspecific necrotizing arteritis and periarteritis. Note edematous anuclear wall of small artery and almost complete occlusion of lumen. The kidney parenchyma about vessel is also anuclear.

FIG. 5. (lower) Complete obliteration of lumen of medium-sized artery of kidney. Occasional giant and epithelioid cells are still present in the fibrous tissue thrombus. Note interruption of elastic membranes at various points (I) and proliferation of same at others (P). Elastica Van Gieson stain. This vascular change resembles the surgical biopsy of lymph node taken eight months before death except that the thrombus was more granulomatous.

Pituitary: There appeared to be small foci where the cellular elements showed varying stages of degeneration from swelling of the cells and hyalinization thereof to pyknosis and disintegration. Basophilic cells were prominent but they did not supersede the eosinophilic variety. The pars nervosa was not remarkable.

Skin: The architecture was well preserved. There was no specific process in the sections studied or noticeable vascular changes.

Brain: (Frontal, occipital lobes, internal capsule pons). The piaarachnoid over the occipital lobe was infiltrated with histiocytes and round cells. Scattered throughout the brain were solitary nodules composed of either a central giant cell or capillary and surrounded by

exudate of epithelioid-fibroid type of cells. In some instances, the central vessel was obliterated by similar exudate. In the medulla, the Virchow Robin space about small vessels were surrounded by cuffs of histiocytes, round cells, pus cells, plus a small zone of necrosis eccentrically located. This exudate extended into the wall of the vessel, at times obliterating the lumen. The parenchyma surrounding the vessel was also involved with a similar exudate. Fat stain revealed a yellow staining material in some of the capillaries of the cortex free in the lumen as well as in the endothelium of the capillaries. No fat was found about the capillaries, free or within so-called gitter cells.

Cervical cord: A small nodule was noted in the commissure composed of a central coagulation necrotic zone and periphery of swollen histiocytes and round cells. Some of the vessels showed cuffing with a hyaline degeneration of the vessel wall and narrowing of the lumen (figure 6). This was found in both gray and white matter.

There was a pale pinkish blue (hematoxylin and eosin) matrix scattered throughout the bone marrow, arranged in irregular alveoli suggestive of the old fat spaces. Fat was practically absent. There was marked myelopoiesis but the shift was decidedly to the right. Erythropoiesis was rare, the relation being about 10:1. There were peculiar giant cells,

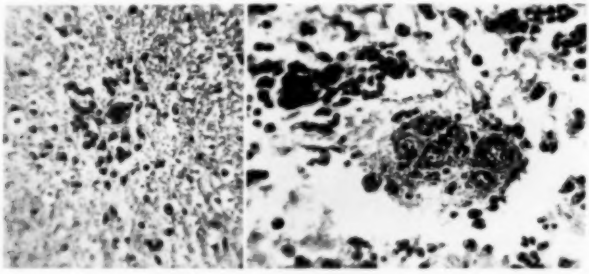

FIG. 6. (left) Cervical cord with perivascular cuffing and hyaline degeneration of vessel wall and marked narrowing of lumen.

FIG. 7. (right) Bone marrow showing small arteries with thickened walls and narrowed lumina.

some containing bizarre nuclei with pyknotic chromatin, others were multinucleated and resembled a foreign body type, yet there were no definite granuloma of a specific process. Vascular changes were prominent in that small arteries showed marked narrowing of their lumina as a result of internal proliferation, the lumen to wall ratio being 1:4 (figure 7).

First metatarsal bones: (Head, left and right). On gross inspection of the slide, one immediately noted that the left was more delicate in its architecture than the right. The articular cartilage of the left was one-half to one-third the thickness of that on the right. An enchondral zone of calcification was distinct but narrow. The bony trabeculae were about one-half to one-third the thickness of those on the right. The periosteum of the left, however, was greatly thickened as compared to the right, in places being two to three times as thick and composed mainly of what appeared to be a hyalinized connective tissue. The bone marrow in both was fatty and showed very little response. The larger vessels present in the section of the left showed thickened walls, some as a result of hyperplasia of the intima. The lumen to wall ratio at times was 1:1 on both sections. No specific process was noted in left or right metatarsal bones.

Bacteriological Studies

Ziehl-Neelsen stain of smears from the lung and sections of lung, kidney, liver, spleen, and lymph nodes revealed no acid-fast bacilli. Methylene blue and MacCallum's stains

for bacteria revealed bizarre gram-negative bodies in some of the cells of the reticuloendothelial system, especially of the lymph nodes, but the identity of these bodies was not certain. Cultures from the unconcentrated hilus lymph nodes on egg media were negative for tubercle bacilli after twelve weeks of observation. Culture of the lung after concentration in 4 per cent sodium hydroxide and neutralized with 15 per cent hydrochloric acid was negative for tubercle bacilli after twelve weeks. Emulsions of the hilus lymph nodes were cultured on blood agar, brain infusion broth, and endos media. A number of banal type of organisms were isolated, the identity of which shall be discussed in a subsequent paper.

Animal Inoculations

Emulsions made of the hilus lymph nodes were injected in 0.1 ml. amounts in 8 different skin sites of 2 guinea pigs. Another 2 guinea pigs were inoculated with 1.0 ml. of the emulsions intraperitoneally. The animals were tuberculin tested with 10 mg. of O.T. at intervals of three to six weeks. These reactions were strongly positive in all animals at both testings. Skin biopsies were taken at weekly intervals for three weeks and then again at six weeks. The lesions of the skin developed slowly and at three weeks varied in size from .5 to 1.0 cm. but regressed to some extent although not completely six weeks after the inoculation. The animals died of enteritis which was present in many of the noninjected animals as well. Microscopic sections of the skin biopsies revealed a nonspecific inflammatory type of reaction with pus cells and histiocytes but no giant cells.

Postmortem Examination of the Animals

Intradermally inoculated group: The lymph nodes draining the skin near the site of inoculation were enlarged, contained gray yellow nodules that were firm but were not caseous. The liver and spleen were enlarged showing an occasional yellow gray nodule up to 3 mm. in diameter. The lung and hilus lymph nodes were not remarkabe.

Microscopic examination (guinea pig 45-24): There were small foci of necrosis, without cellular response in the liver. However, there were specific nodules with central coagulation necrosis and epithelioid cells surrounding it in which an occasional round cell was scattered (figure 8a). The spleen was studded by numerous nodules, discrete and confluent, of epithelioid cells in which an occasional giant cell was noted. No reaction about these nodules was found. About 50 to 75 per cent of a lymph node situated at the crest of the ilium (figure 8b) was replaced by a specific process composed mainly of histiocytes arranged in nodules either discrete of confluent. An occasional giant cell was noted (figures 9a, b). There was no specific involvement of the kidney. A suspicious nodule composed of epithelioid cells and round cells with a suspicious giant cell was found surrounding a capillary in the lung (figure 8c). Fifty per cent of the peritracheal lymph nodes was replaced by a specific process composed of epithelioid cells with few other types of cells. Giant cells were rare. Reactive phenomena were practically absent. Deep in the cutis was a perivascular accumulation of round cells and histiocytes, nonspecific in character. There was no specific involvement of the pancreas but a peripancreatic lymph node was replaced to the extent of 75 per cent of a specific process composed of discrete and confluent nodules, some showing marked central fibrinoid necrosis in which nuclear debris was prominent. Giant cells were scarce. There was a marked epithelioid reaction and very little response about the nodule. Ziehl-Neelsen stain revealed acid-fast bacilli in liver, spleen, all lymph nodes, and lung.

Microscopic examination (guinea pig 45-22): The nodules in the spleen had central coagulation necrotic areas in which there was cellular debris and were surrounded by an epithelioid-like reaction in which granulocytes and lymphocytes were also intermingled. In the liver there were discrete nodules composed of centrally degenerated areas surrounded by epithelioid cells, granulocytes, and lymphocytes. Some of the areas presented calcifica-

tion centrally. No remarkable changes, vascular or otherwise, were noted in the kidney. Scattered throughout the cortex of the peritracheal lymph nodes were discrete and con-

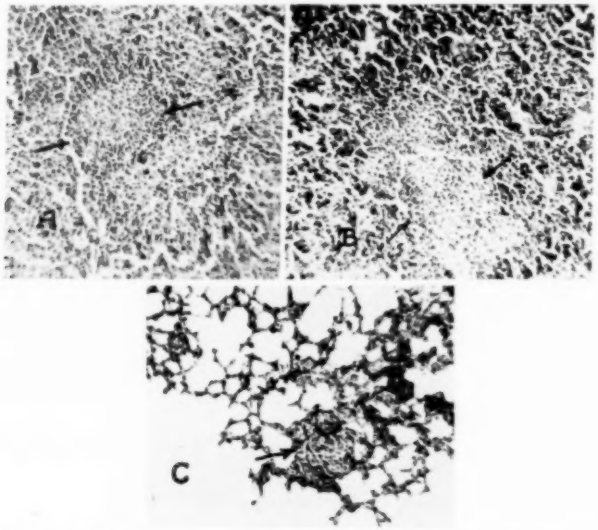

FIG. 8. Guinea pig (intracutaneous group). Miliary nodules of liver (A), spleen (B), and lung (C). The lesions are composed mainly of swollen histiocytes and an occasional giant cell. Note absence of reaction about the nodules.

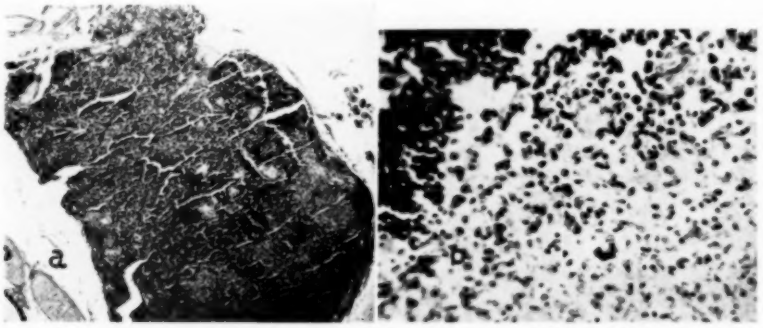

FIG. 9a. Section of entire lymph node of guinea pig. Note diffuse involvement of about one-third of cortex and medulla (D) and miliary nodules (M) in remainder of node. The marginal sinuses are free from pathology.

FIG. 9b. High power. Note granulomatous lesion composed of swollen histiocytes, few round polymorphonuclear cells, and central giant cell.

fluent nodules composed of epithelioid cells which involved particularly the follicles. An occasional giant cell was noted. In addition to the epithelioid cells were scattered polymorphonuclear leukocytes. There was no reaction about these nodules. They did not in-

vade the cortical sinuses which were free. Some of the nodules had accumulations of pus cells centrally, many of which were degenerated. The position of the lesions and the nature of the reaction, except for pus cells, simulated very closely those found in the lymph nodes of the patient. Examination of two sections of the lungs failed to reveal any specific changes. Ziehl-Neelsen stain revealed acid-fast organism in the spleen and peritracheal lymph nodes.

Only one of the animals inoculated intraperitoneally was examined post mortem. The spleen was slightly enlarged and presented occasional yellow gray nodules without evidence of gross caseation. There were no other remarkable findings.

Microscopic examination (guinea pig 45-23): There were several nodules in the spleen which were confluent, composed of epithelioid cells for the most part in which an occasional round cell and giant cell was dispersed. One of the nodules had a central area suggestive of coagulation necrosis. In the peritracheal lymph nodes there were small zones, especially in the cortex, composed of epithelioid cells which did not form distinct nodules. There were no specific changes in the lung or liver. Ziehl-Neelsen stain revealed acid-fast organism in the spleen.

Lesions of the organs of each animal were pooled, emulsified, and concentrated (4 per cent sodium hydroxide neutralized with 15 per cent hydrochloric acid) and spread over egg media. No growth occurred after six weeks of incubation.

Anatomical Diagnosis

1. Sarcoidosis, generalized, involving lungs, kidneys, liver, peritracheal, peribronchial, and hilus lymph nodes, and brain and meninges.
2. Panarteritis and periarteritis of small and medium-sized arteries, generalized, sarcoid, and nonspecific in character.
3. Emboli, fat, of glomeruli and capillaries of brain.
4. Infarcts, ischemic, of both kidneys.
5. Encephalitis, disseminated, and myelitis.
6. Osteoporosis of first metatarsal and thickening of periosteum, left.
7. Bronchiectasis, focal, saccular, with cyst formation, of both lungs.
8. Bronchopneumonia of entire lung and lower lobe of left lung.
9. Atrophy, fibrotic, of spleen.
10. Atrophy and fibrosis of both epididymides and testicles.

DISCUSSION

This typical case of sarcoid, in which the tuberculin test remained negative throughout, presented almost every form of disease heretofore described plus renal manifestations which were hitherto unreported. Thus, there were syndromes related to the eyes, parotid glands, skin, bone, central nervous system, and miliary involvement of virtually every organ in the body. The lesions of the kidneys were primarily vascular, with specific granuloma surrounding and/or invading the medium-sized and small arteries, occluding some to a marked degree (panarteritis and periarteritis). These vascular occlusions led to infarcted areas of necrosis of the parenchyma of the kidney. In addition to the specific changes, there were nonspecific alterations of the small arteries that appeared to be more recent. There was diffuse necrosis of the entire wall which in some instances extended to the perivascular tissue. Vascular changes were present in other parts of the body. The small arteries of the central nervous system were for the main part surrounded by round cells, some having edematous walls, others showing complete necrosis of the walls. The bone marrow and epididymis presented thickened walls and narrowed lumina of small arteries. The small arteries leading to the lymph nodes presented invasion by specific granuloma, with occlusions of their lumina. Involvement of the kidney by miliary sarcoid nodules has been described frequently, but clinical symptoms related to the kidneys in sarcoidosis have been rare. Azotemia has been reported in 4 cases with nonprotein nitrogen values up to 90

mg. per 100 cc. (1, 2, 3, 4). These findings were not associated as a rule with an elevation of the blood pressure (154 systolic and 115 diastolic in one case) (3). The urines in these cases had a low specific gravity (1.006 to 1.012) with albumin and casts. Only one of these cases came to autopsy (2). The kidneys were somewhat smaller than normal with a granulomatous surface. Miliary sarcoid nodules as well as caseating nodules of tuberculosis were found on microscopic examination. In the case here reported the terminal picture was that of a malignant hypertension with uremia. The highest nonprotein nitrogen (post mortem) was 360 mg. and the creatinine 4.5 mg. per 100 cc. The etiology of the hypertension can be ascribed to the occlusion of the medium-aized arteries by specific sarcoid granuloma, simulating the Goldblatt type of kidney. The occlusion of the arteries, however, was complete in many instances and resulted in multiple anemic infarcts. The nonspecific thickening of the walls of the small arteries associated with the narrowing of the lumina, as noted in other parts of the body (bone, marrow, epicardium, epididymi), is probably related to the hypertension. The necrosis of the walls of the small arteries in the kidneys as well as in other organs appeared to be a more recent process as it was not observed in the nodes removed surgically eight months before death of the patient. At that time there was specific granulomatous involvement of the arteries. It is difficult to determine whether or not the necrotizing arteritis was related to the hypertension, the sarcoid specifically (5), or to a terminal hyperergic state (6). Necrotizing arteritis has been described in all three conditions. Staehlen (5) reported necrotizing arteritis and periarteritis nodosa in a case in which the sarcoid-like pathology originated in the nose, extended directly to the brain, and finally metastasized to the rest of the organs. Similar findings were observed by Weinberg and Gartside (8), Rossle (9), and Teilum (10). The cyst-like cavities of the lungs here described were mentioned in only two reports (11, 12). Rubin and Pinner (11) considered the process to be on an emphysematous basis. The studies here presented using special connective tissue stains indicate that it is bronchiectatic in character resulting from peribronchial fibrosis and loss of elastic tissue. The absence of involvement of the afferent lymph channels and the marginal sinuses by the granulomatous process in the vast majority of the lymph nodes studied in this case makes this feature an aid in the differential diagnosis of sarcoidosis and tuberculosis. Except in miliary tuberculosis of the lymph nodes, invasion of the nodes is usually by way of the lymphatics with tubercles in the marginal sinuses. In sarcoid this is rare, as the disease in the nodes is most likely on a hematogenous basis. In examining many surgical specimens this fact was borne out. Rarely there may be extension of the cortical process into the marginal sinuses. The significance of Sudan III staining material in the capillaries of the glomeruli and in the endothelium proper, as well as in the lumen and the endothelium of the brain capillaries, and the near depletion of fat in the bone marrow sections studied is not completely understood. This subject will be discussed in a subsequent paper where experimental studies in animals gave a possible clue.

The most unusual findings were the lesions in the guinea pigs injected intradermally and intraperitoneally with an emulsion of the hilus lymph nodes. Weekly biopsies of the skin of the former for three weeks and one at six weeks showed no specific pathology but the lesions persisted for six weeks. The tuberculin test was strongly positive in both groups of animals after three and six weeks using 10 mg. O.T. Upon the death of the animals six weeks after inoculatiou, gross and microscopic lesions of the lymph nodes, liver, spleen, and lung were suggestive of sarcoidosis. This was especially true of the intradermally injected animals. Here, as in humans, the involvement of the lymph nodes excluded the marginal sinuses. Ziehl-Neelsen stains revealed numerous acid-fast bacilli in the liver,

spleen, lung, and lymph nodes. Cultures of these organs on egg media were negative for tubercle bacilli. The hilus node of the patient was used for the inoculation because it was one that was extensively involved and was large enough to serve for entire experiment of cultures, smears, and animal inoculations. There was no evidence of tuberculosis in this node as noted by microscopic section, smears, and numerous cultures of the digested and undigested material. Search for the tubercle bacilli in the human material whether by microscopic section, smears, or cultures was entirely negative. Cultures of the lymph nodes on brain infusion broth, blood agar, and thioglycolate media did yield a group of banal type of organisms which shall be discussed in a later paper. In the histologic sections, unidentified gram-negative bodies were found in the cells of the reticulo-endothelial system of the lymph nodes by methylene blue and MacCallum's stains for bacteria.

SUMMARY

1. A case of Boeck's sarcoid is described with the unusual features of generalized specific arteritis and periarteritis as well as nonspecific necrotizing arteritis. Associated with the above were hypertension and uremia.

2. Sarcoid material injected intradermally and intraperitoneally into guinea pigs produced a hyperergy to Old Tuberculin and lesions of the lung, liver, spleen, and lymph nodes that closely resembled sarcoidosis. Numerous acid-fast bacilli were found in the lesions but cultures of the organs were negative for tubercle bacilli.

3. A banal group of organisms was isolated from human sarcoid material and will be elaborated upon in a later report.

SUMARIO

Estudios Patológicos y Experimentales del Sarcoides de Boeck. Comunicación de un Caso con Panarteritis, Periarteritis e Hipertensión y Uremia Terminales, y Reproducción de una Lesión Sarcoidea en Cobayos

1. El caso de sarcoides de Boeck descrito mostraba las características extrañas de arteritis y periarteritis específicas generalizadas así como de arteritis necrosante anespecífica, habiendo además hipertensión y uremia.

2. La sustancia sarcoidea inyectada intradérmica e intraperitonealmente en cobayos produjo hiperergia a la tuberculina antigua y lesiones de los pulmones, hígado, bazo y ganglios linfáticos, muy semejantes a sarcoidosis. Aunque se encontraron numerosos bacilos tuberculosos en las lesiones, los cultivos de dichos órganos fueron negativos para dichos bacilos.

3. Del material sarcoideo humano se aisló un grupo de microbios banales que se comentará más a fondo en un informe subsiguiente.

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ERYTHEMA INDURATUM BAZIN[1]

Report of a Proved Case Associated with Tuberculous Lymphadenitis, Completely Relieved by Tuberculin Desensitization

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INTRODUCTION

The literature on the subject of erythema induratum has been rather scant in recent years. It consists mainly of brief remarks dealing with clinical diagnostic features in transactions of dermatological societies, with only an occasional mention of unsuccessful therapy. The internist, apparently, is little acquainted with this entity, notwithstanding the fact that erythema induratum is merely a reflection of a systemic disease process.

The purpose of this report is to consider some etiologic and pathologic factors of Bazin's disease and to demonstrate the feasibility of a therapeutic success by means of desensitization with Old Tuberculin, for some reason a forgotten therapeutic agent.

Comparatively little has been added to the original description of erythema induratum by Bazin (1) in 1861. He pointed out that the red indurated plaques are prone to develop in girls of scrofulous constitution, that they appear commonly on the legs, although they might occasionally occur elsewhere, that these plaques are never itchy and seldom tender. These clinical features, however, are apparently insufficient for diagnosis by themselves, as there are other nontuberculous conditions which may give rise to nodular erythematous lesions within the skin and subcutis with which erythema induratum might easily be confused, *e.g.*, erythema nodosum (2). Moreover, Montgomery and his associates (3) pointed out that somewhat similar lesions clinically may also develop on the basis of vasculitis and that still others, previously reported as instances of erythema induratum, are more properly classed with the so-called sarcoid lesions of the skin. Obviously, an accurate diagnosis is essential for a fair therapeutic evaluation. It is particularly important when the therapeutic aim lies further than the local expression of the disease, and the therapeutic agent requires considerable caution in its administration.

REPORT OF CASE

First admission: The patient, a 35 year old former Viennese dancer, was admitted to this hospital for the first time on October 3, 1939, complaining of painful red nodes on her legs associated with swelling of the ankles, and also of some lower abdominal pain. She stated that she had had "ovarian trouble" since the age of 19, with exacerbations from time to time. She had also had leukorrhea for many years. In 1931 she had "dry pleurisy." During the year prior to admission, she had lost five pounds in weight. The menstrual cycle was normal. The history was not significant otherwise.

The lesions on her legs, which constituted the major complaint, had first appeared in 1929 as erythematous, hard, tender lumps about both ankles. At that time, tonsillectomy was done and the patient also received some heat treatment. The lesions, however, persisted some months after the tonsillectomy and then regressed spontaneously, although the patient claimed that she was "always sick with her legs" during this period. The lesions again recurred in 1932, lasted several months, and again disappeared spontaneously. She had two more recurrences of the same difficulty in 1936 and in 1937, for which she received

[1] From the Medical Service and Division of Laboratories of the Hospital for Joint Disease, New York, New York.

baking and mud treatment in Carlsbad. Each time the lesions lasted several months in spite of therapy, and then regressed. The most recent recurrence, for which she was admitted to this hospital, took place in August 1939. With each crop of tender nodes on her lower legs, swelling about the ankles appeared, especially during activity. It should be noted that the occurrence of the lesions was not related to the menstrual cycle and was apparently independent also of the season of the year.

Physical examination: The eyes, including the fundi, were negative. The upper teeth were replaced by a plate; the lower gums were tender. Examination of the heart and lungs revealed nothing abnormal. The blood pressure in mm. of mercury was 95 systolic and 60 diastolic. Palpation of the abdomen revealed slight tenderness in both lower quadrants and on pelvic examination there was noted a diffuse tender induration, the size of a fist,

FIG. 1. Photographs showing the presence of multiple indurated nodes on the posterior and lateral surfaces of both legs. These nodes were tender and many of them, though not all, were erythematous. Some swellnig of the ankle regions was also present.

situated to the right of the midline and limiting the mobility of the uterus. Neurologic examination was negative except for absence of the left knee jerk. On the posterior and lateral surfaces mainly of both legs, there were a number of erythematous areas, varying in size from 1 to 2 cm. in diameter and, beneath them, tender indurated nodes were palpable. Nodular indurations could also be felt in other areas on the calves, where the overlying skin was not erythematous. Some edema of the ankles was present (figure 1). Aside from the legs, only a single nodule on the lateral surface of the right arm was observed.

The laboratory findings were not significant except for an increased sedimentation rate, varying between 13 and 50 mm. in 45 minutes. The Kahn and Kline tests were negative. A smear of the cervix was negative. Roentgen examination of the chest failed to show any evidence of old or recent tuberculosis. Roentgenograms of the bones of the lower extremities were negative. The tuberculin test was positive in dilution of 1:10,000, but was negative in higher dilution.

During the patient's stay in the hospital, the temperature remained below 100° F. On

the tenth hospital day, the patient presented two white-centered papular lesions on the left index finger, which later became purplish and, subsequently, wart-like in appearance. The patient recalled having had such lesions previously on her palms. After several days, the lesions on the lower extremities became paler, less indurated, and somewhat scaly, and the tenderness abated. However, there was a tendency for new lesions to appear. At about this time also, an eruption of small red papules appeared on the right buttock. While in the hospital the patient received twenty short wave treatments to the pelvis, and was discharged on November 10, 1939. A tentative clinical diagnosis of erythema induratum was made by one of us (T.T.F.), although some observers leaned toward the impression of erythema nodosum. It was felt also that the erythematous skin lesions were somehow associated with the pelvic condition.

Second admission (November 24, 1939 to February 10, 1940): The second admission was prompted by the appearance of a painful node above the medial portion of the left clavicle and the recurrence of a fresh crop of tender indurated nodules, many of them erythematous, on the upper, as well as on the lower, extremities, including one on a finger. Examination revealed a group of tender, enlarged supraclavicular lymph nodes. The chest was clear. The patient was again afebrile. From time to time, additional small, firm, tender, subcutaneous placques appeared on the limbs and tended to regress after 12 to 48 hours. The tuberculin test was repeated and found definitely positive in dilution of 1:10,000, slightly positive in dilution of 1:100,000, but negative in higher dilution.

First skin biopsy: On December 7, 1939, a biopsy of a nodule on the right leg was done. The specimen consisted of a small piece of skin and a few bits of subcutaneous fat tissue. Sections of the cutis showed slight keratosis, subpapillary fibrosis, and perivascular infiltration with lymphocytes, mononuclear cells, and an occasional polynuclear leukocyte. More significant changes were observed in the subcutaneous fat tissue. Within the latter, there were numerous focal, discrete, or conglomerate nodules composed largely of epithelioid-like cells and infiltrated by lymphocytes, scattered polymorphonuclear leukocytes, and a number of eosinophils. Some of these nodular foci contained small giant cells. A few of them presented suggestive areas of necrosis. While they had some resemblance to tubercles, their morphology was by no means typical. The adjacent fatty tissue showed fibrosis and infiltration by inflammatory cells. No vascular lesions of any kind were observed. By way of diagnosis, it was stated at the time that the findings were not those generally associated with erythema nodosum. While the specific diagnosis of erythema induratum was not made, the opinion was expressed that the condition might conceivably represent some peculiar expression of tuberculous reaction within the subcutaneous fat tissue (figure 2).

First lymph node biopsy: On December 20, 1939, an enlarged lymph node from the left supraclavicular region was removed for biopsy. At the same time some of the pertinent tissue was used for guinea pig inoculation. The guinea pig was sacrificed after ten weeks and showed no evidence of tuberculosis. Sections of the lymph node showed its architecture to be completely altered and replaced by a pleomorphic cellular tissue rich in fibroblasts. Dispersed within this tissue were numerous cells, apparently of reticulum cell origin, with peculiar large oval nuclei and large eosinophilic nucleoli. Many of these cells were multinuclear. The histologic picture presented by this lymph node was regared as being very suggestive of Hodgkin's disease (figure 4A).

Second skin biopsy: On February 1, 1940, a biopsy was again taken of a subcutaneous nodule on the left leg. The specimen consisted of several small bits of somewhat indurated, subcutaneous, fat tissue. These showed merely a few focal collections of chronic inflammatory cells, principally around the smaller blood vessels.

While in the hospital, the patient received several roentgen treatments over the lower extremities without apparent benefit, and she was referred to the Outpatient Department for further observation. In the course of the next several months, she received additional X-ray therapy directed against the constantly recurring lesions on the lower extremities without demonstrable effects, and the administration of liver extract and vitamin preparations was likewise ineffectual.

Third admission (October 15, 1940 to November 15, 1940): The patient again returned,

presenting on the extensor surfaces of both calves numerous red, warm, tender areas which were indurated and raised above the surface of the skin. A few similar lesions were present also on the thighs. There was a coalescence of these areas about the ankles, with general induration but no edema. On the arms, a few irregular subcutaneous placques were palpable, and over both elbows there were reddened, glistening, papular, circular lesions, which were psoriasis-like in character. It was thought by some observers that the spleen was enlarged. The laboratory findings were essentially as previously recorded.

Third skin biopsy: Still another biopsy of a nodule on the left leg was taken on November 2, 1940. The specimen consisted of several bits of subcutaneous fat tissues, one of which was covered over by a strip of skin. The fat tissue was somewhat indurated and in places presented a number of grossly discernible, small, yellowish, miliary nodules. Microscopic sections showed essentially the same findings that were observed in the previous biopsy

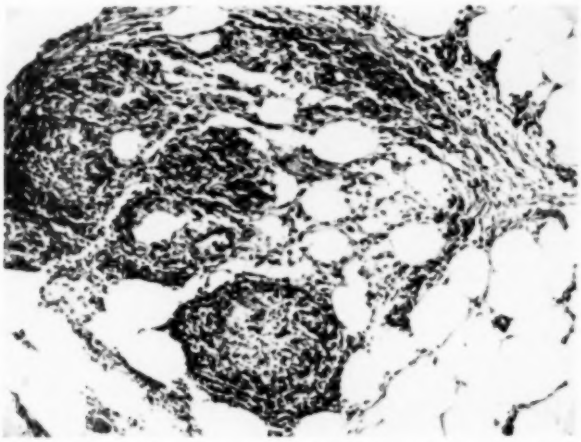

FIG. 2. Photomicrograph of a representative field in the subcutaneous fat at the site of a biopsied, indurated, and erythematous node. Within this field there are several contiguous nodules composed largely of fibroblastic and histiocytic cells and infiltrated by lymphocytes and occasional polymorphonuclear leukocytes, including some eosinophils. The adjacent fat tissue showed recent necrosis in places, beginning fibrosis, and infiltration by inflammatory cells. × 100.

specimen. The lesions were distributed throughout the subcutaneous fat tissue principally in the form of clusters of miliary nodules, some of which had a superficial resemblance to tubercles. Concerning the evolution of the lesion in question, it was stated that the latter apparently began as a subacute inflammatory focus infiltrated by small round cells and leukocytes, among which eosinophils were prominent. The fat cells in the involved areas were modified and were even replaced by foam cells. This was accompanied by the appearance of histiocytes and fibroblasts, resulting in the development of numerous discrete and conglomerate nodules. Multinuclear giant cells were prominent in relation to some of the nodules. Eventually, the lesion appeared to regress, leaving only fibrous scars and scattered small nests of foam cells as residua (figures 3A and B).

While no definitive diagnosis was ventured on the basis of this biopsy, it was felt that the subcutaneous nodules apparently represented some unusual and peculiar chronic inflammatory condition that was not in itself clearly tuberculous in character. It was suggested, furthermore, that the subsequent course might clarify the clinical picture as, indeed, proved to be the case.

With bed rest, recession of the skin lesions took place although they did not disappear altogether, and the patient was again referred to the Outpatients Department. With resumption of activity, however, she again developed new crops of lesions on the arms and legs. At about this time, the appearance of a group of tender, matted lymph nodes was noted

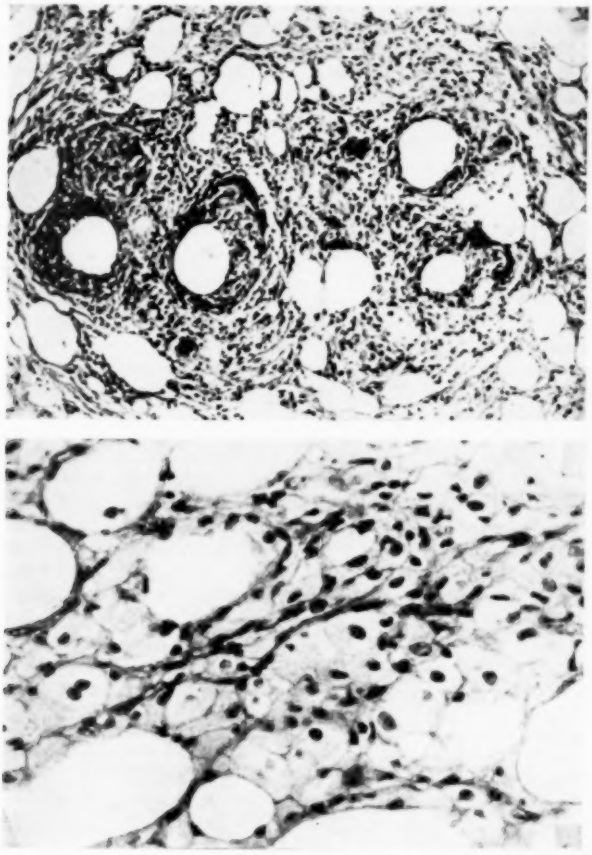

FIG. 3A. (Top) Photomicrograph of a representative field in a subsequent biopsy specimen showing a cluster of histiocytic nodules within the subcutaneous fat tissue. Multinuclear giant cells may be observed in relation to some of these nodules. Within the fat tissue generally, one observes evidences of inflammation and organizing fat necrosis, leading ultimately to fibrosis and the appearance of nests of foam cells. × 100.

FIG. 3B. (Bottom) Photomicrograph of a field from the lesion illustrated in figure 3A, showing a nest of foam cells reflecting the organization of fat necrosis. × 150.

in the left supraclavicular region where a biopsy had been taken previously (the one showing a picture suggestive of Hodgkin's disease). There were also a few palpable lymph nodes in the anterior triangle of the neck, in the left axilla, and in the left inguinal region.

Fourth admission (February 4, 1941 to February 22, 1941): At this time, several enlarged supraclavicular lymph nodes were excised for biopsy, as was also a wedge of skin and sub-

cutaneous fat tissue from the back of the calf where a discrete, hard subcutaneous nodule had been palpable.

Sections of all the lymph nodes submitted showed areas of caseous necrosis and numerous discrete and conglomerate tubercles, clearly indicative of tuberculous lymphadenitis. This impression was verified by guinea pig inoculation (figure 4B).

Fourth skin biopsy: The skin biopsy taken on this occasion revealed an area within the subcutaneous fat, presenting a cluster of tiny, pale yellow nodules, varying in size from pin point to 2 mm. in diameter. Microscopic sections of these lesions showed changes within the fat resembling those described in the previous biopsy, and it was felt that the lesion should be classified under the head of erythema induratum (Bazin), a condition usually held to represent a peculiar cutaneous manifestation of tuberculous infection.

Whereas the nature of the skin lesions and the associated lymphadenopathy now seemed established, it was decided to treat the patient by desensitization to tuberculin. The first dose administered (on April 12, 1941) consisted of 0.1 cc. of Old Tuberculin in a dilution of one to a billion. The injections were given three times a week at two day intervals, the second dose being 0.12 cc. and the third 0.16 cc. Following the third dose, an afternoon rise in temperature to 100° F. occurred and the next dose was therefore reduced to 0.14 cc. The subsequent doses administered were 0.18, 0.24, 0.32, 0.42, 0.54, 0.68, 0.80 and 1.0 cc., respectively. The tuberculin dilution used was freshly prepared each week and, when 1.0 cc. of a given dilution had been reached, a dilution ten times stronger was prepared. No systemic reaction was observed until January 9, 1942 (almost nine months after therapy was instituted), when the patient had a chill and a temperature of 102° F., associated with diarrhea. These untoward manifestations may have been coincidental, however, since treatment was resumed, continuing with gradually increasing doses, without any further difficulty. On February 3, 1942, a dose of 1.0 cc. of undiluted Old Tuberculin was administered. This dose was repeated at weekly intervals on three occasions with no local, focal, or systemic reactions. The treatment was discontinued at this point. In the course of desensitization, the skin lesions and the enlarged lymph nodes gradually disappeared. On February 1, 1943, the tuberculin test was found to be entirely negative with antigens of both human and bovine strains.

The patient was seen subsequently on many occasions and is still under observation. She enjoys good health, is at work, and travels a good deal. Her chest is clear. The pelvic mass which she presented originally is no longer palpable and causes no subjective complaints. At no time has there been any recurrence of the skin lesions or enlargement of lymph nodes. A tuberculin test done recently (December 24, 1947) was definitely positive (human and bovine antigens) in dilution of 1:1,000 and slightly positive in dilution of 1:10,000. Even though the patient is apparently no longer completely desensitized, however, she is still entirely well clinically and over six years have now elapsed since tuberculin desensitization was discontinued.[2]

DISCUSSION

The treatment of erythema induratum by desensitization to tuberculin was enthusiastically advocated as early as 1905 by Whitfield (4), McCall-Anderson (5) and others (6), who pointed out that the condition may respond unusually well to such treatment. Tuberculin therapy is at present largely neglected and many clinicians confronted with the problem of treating erythema induratum are likely to adopt a "laissez faire" attitude or resort to ineffective nonspecific symptomatic treatment, employing ultraviolet and X-ray irradiation, as well as various lotions and ointments. More recently (7), an attempt has been made to treat the condition by chemotherapeutic agents such as promizol and streptomycin, but the use of the latter has apparently not resulted in any lasting benefit.

[2] The patient was last seen by one of us (T.T.F.) on December 28, 1948. She is clinically well. There were no recurrences of the skin lesions.

The current neglect of tuberculin therapy stems largely from unfamiliarity with its benefits, but apparently also from therapeutic failures, some of which, at least, are attributable to inaccurate diagnosis or to faulty judgment and, particularly, to undue haste in planning the course of treatment. As Montgomery, O'Leary and Barker (3) have emphasized, before embarking on a long program of tuberculin desensitization in a suspected case, one should require as evidence of the presence of erythema induratum, in addition to a positive tuberculin reaction: (*1*) biopsy of one or more cutaneous erythematous nodes showing the histopathologic picture associated with the condition; and (*2*) proof, or at least presumptive evidence, of active tuberculosis elsewhere in the body.

As for the therapeutic management, it cannot be emphasized too strongly that tuberculin desensitization, if it is to be effective, must be prolonged and cautiously administered, preferably by a single observer, carefully avoiding even slight local or systemic reactions. So planned and administered, the method is not hazardous, as some have apparently felt. In the present case, the initial dose of Old Tuberculin, as noted, was no more than 0.1 cc. of a dilution of 1:1,000,000 (1:10 (9)) and the increments were so small that almost a year was required to achieve gradual desensitization. During that period, only one febrile episode was noted, during the ninth month of treatment. Indeed, even this episode may have had no relation to the tuberculin therapy, since the latter was resumed shortly thereafter without any untoward reaction. The rationale for tuberculin desensitization is the elimination of undesirable and disturbing allergic manifestations and the furtherance thereby of natural immunologic control of the tuberculous infection. On the other hand, we do not intend to convey the impression that tuberculin desensitization will invariably result in as gratifying a clinical response as was obtained in the case reported. Obviously, the result will also depend largely on the virulence of the infecting organism, a variable factor that can be determined only empirically (8). Furthermore, it appears that there are occasional patients who are so exquisitely sensitive to tuberculin that they seem incapable of being completely desensitized (9). There is a possibility that the favorable therapeutic response in our case was due in a measure to the fact that our patient *never was* very sensitive to tuberculin.

It may be questioned by some, since erythema induratum is a condition characterized by spontaneous remissions, whether tuberculin desensitization is to be credited with the gratifying clinical result in this case. That is a valid reservation, to be sure, but in support of our view it may be pointed out that the patient has remained completely free of all clinical manifestations of her disease for the past six years, whereas previously she had never been entirely free of complaints at any time, and during the two years preceding tuberculin therapy had been developing recurrent crops of erythematous nodes with great regularity.

The Hodgkin-like picture observed in the supraclavicular lymph nodes prior to the development of indubitable tuberculosis within the same group of nodes, is of unusual interest (figure 4A). The eight year interval that has now elapsed without the appearance of any manifestations of Hodgkin's disease and the continued good health of the patient would seem to exclude fairly conclusively any possibility of Hodgkin's lymphoma. On the other hand, the relevant lymph nodes apparently did not contain tubercle bacilli at that time, inasmuch as guinea pig inoculation was negative. It is equally certain that the lymph nodes reappearing subsequently at the same site did show tuberculous infection since the pathologic evidence, already clearly indicative of caseating tuberculosis, was further substantiated by repeated guinea pig inoculation (figure 4B). In all probability, we are dealing with a peculiar and unusual hyperplastic forerunner of tuberculous lymphadenitis.

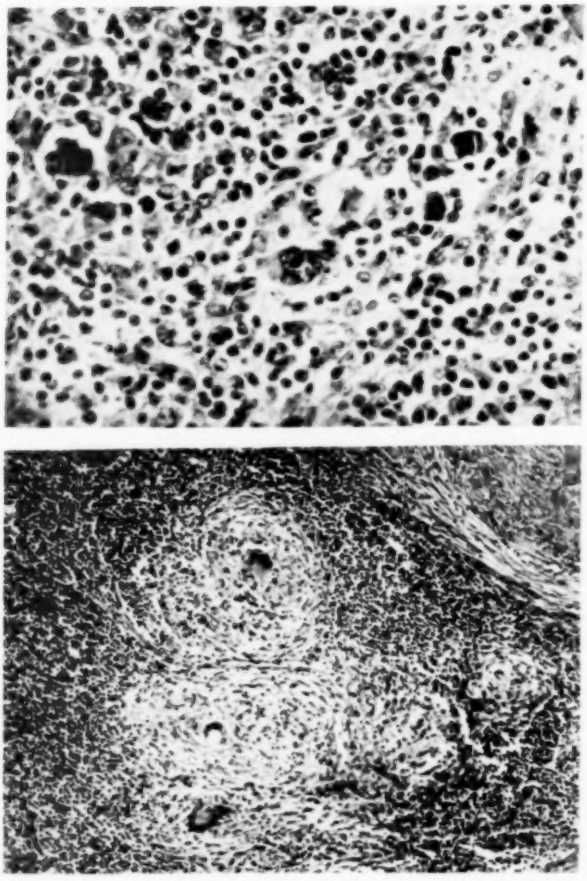

FIG. 4A. (Top) Photomicrograph of a field from supraclavicular lymph node (first biopsy) showing complete replacement of normal architecture by a pleomorphic cellular tissue. The latter contained numerous mononuclear and multinuclear cells, apparently of reticulum cell origin, presenting large pale nuclei with reddish nucleoli. It was the appearance of these cells particularly that suggested the possibility of Hodgkin's disease. × 500.

FIG. 4B. (Bottom) Photomicrograph of enlarged lymph nodes which recurred at the same site about a year later, showing clear-cut, caseating, tuberculous lymphadenitis. × 75.

SUMMARY

This paper deals with a pathologically proved case of erythema induratum (Bazin), associated with tuberculous lymphadenitis, in which an apparent "cure" was obtained by gradual desensitization with tuberculin. The patient has been followed clinically for over

eight years, during the last six years of which she has remained free of all clinical manifestations of the disease. The histopathologic picture of the cutaneous lesions in various stages of their evolution is described. The cutaneous lesions, at least as they manifested themselves in this case, seem to represent a peculiar, recurrent form of nodular panniculitis, developing apparently as a reaction to tuberculous toxins or allergens elaborated elsewhere in the body.

The development of tuberculous lymphadenitis was preceded by a peculiar hyperplastic reaction in the same group of lymph nodes, which simulated Hodgkin's disease.

SUMARIO

Eritema Indurado (Bazin). Comunicación de un Caso Comprobado Asociado con Linfadenitis Tuberculosa y Completamente Aliviado con la Desensibilización con Tuberculina

Este trabajo versa sobre un caso comprobado patológicamente de eritema indurado (Bazin), asociado con linfadenitis tuberculosa, en el cual se obtuvo una "curación" aparente mediante la desensibilización gradual con tuberculina. La enferma ha sido mantenida en observación clínica por más de ocho años, durante los últimos seis de los cuales ha permanecido sin la menor manifestación clínica de la dolencia. El cuadro histopatológico de las lesiones cutáneas en varias etapas de su evolución es descrito. Dichas lesiones, por lo menos tal como se manifestaron en este caso, parecen representar una forma recurrente, peculiar de paniculitis nodular que constituye aparentemente una reacción a las toxinas o los alergenos tuberculosos elaborados en alguna otra parte del organismo.

La aparición de linfadenitis tuberculosa fué precedida de una peculiar reacción hiperplásica en el mismo grupo de ganglios linfaticos, que simuló enfermedad de Hodgkin.

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PULMONARY ADENOMATOSIS[1]

Report of a Case

BENJAMIN FREEDMAN

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INTRODUCTION

Pulmonary adenomatosis is a diffuse neoplastic disease of the lungs, affecting the bronchiolar and alveolar lining cells. It is regarded as a relatively uncommon disease in man. In 1947, Simon (1) reported a case of pulmonary adenomatosis in man, at which time he stated that ten cases had been previously reported, in all of which, except one, the diagnosis was established at autopsy. Hildebrand (2), in a later report of a case, estimated that a dozen cases of this disease had been reported. It is very likely that more cases of this disease exist than the literature would lead us to expect. Especially because of its resemblance to pulmonary tuberculosis and the fact that some of these cases must find their way to tuberculosis hospitals, a greater awareness of the disease on the part of sanatorium physicians should disclose a higher incidence.

Although the disease bears some pathological similarity to a disease of sheep, variously known as Jaagsiekte, epizootic adenomatosis, and infectious adenomatosis, a relationship between the two has not been established.

Jaagsiekte, as pointed out by Dungal (3), was found to be infectious and due to a pneumotropic virus, strictly limited to the lungs and bronchi of sheep, and transmitted through the expiratory air. No such transmissibility in man could be ascertained.

Pulmonary adenomatosis in man has the characteristics of a multicentric neoplastic process. Taft and Nickerson (4), in considering the relationship of this disease to carcinoma of the lungs in general, were of the opinion that no significance could be attached to this relationship. The majority of lung carcinomas, being bronchogenic in origin, arise from the bronchial or bronchiolar lining. Although some question exists as to the focus of origin of pulmonary adenomatosis, it is thought that it arises from the alveolar lining cells. Histologically, however, there is no sharp demarcation between the alveolar lining and the bronchiolar lining, so that origin from the goblet cells of the bronchiolar mucosa cannot be excluded and, with this in mind, a classification of terminal bronchiolar carcinoma would be tenable. This is especially important when it is considered that one of the basic symptoms is the expectoration of large quantities of thin, mucoid sputum, produced by the goblet cells.

As was indicated by Newberger and Geever (5), roentgenologic and bronchoscopic studies are of major importance in direct and differential diagnosis. If the roentgenographic and clinical picture suggests a diffuse pulmonary neoplasm and bronchoscopy discloses no involvement of the bronchial tree, the diffuse form of alveolar tumor should be considered, especially where the clinical picture presents a recurrent bronchopneumonic process (6).

The following case report brings into evidence certain clinical features, which may provide some enlightenment regarding symptomatology, clinical course, and pathological findings. As was stated above, the recurrent pneumonic crises and the history of expectoration of large quantities of thin, mucoid sputum, are particularly worth recording.

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[1] From Pawling Sanatorium, Rensselaer County, New York.

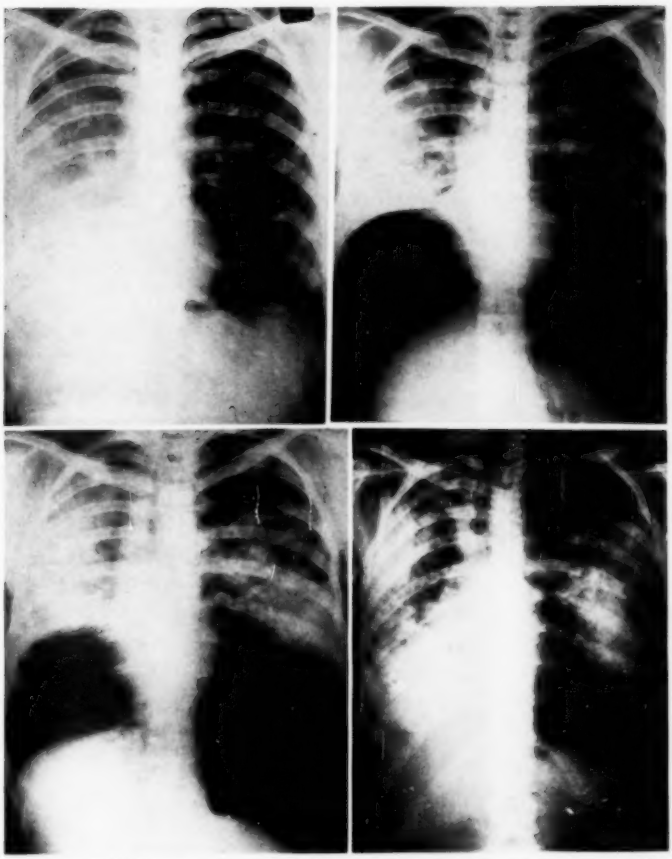

FIG. 1. (Upper left) Roentgenogram of October 30, 1946, when patient attended the outpatient clinic and a tentative diagnosis of pulmonary tuberculosis was made.

FIG. 2. (Upper right) Film of February 13, 1947, showing an established pneumoperitoneum.

FIG. 3. (Lower left) Film of May 6, 1947, following a pneumonic episode.

FIG. 4. (Lower right) Film of September 16, 1947. Last roentgenogram before death, indicating the progressive character of the lesion.

CASE REPORT

The patient, Mrs. E. W., was a 29 year old white housewife. Her family history was not significant. Except for usual childhood diseases before the age of 9, she had always been in good health.

In the eighth month of pregnancy, in July 1946, the patient suddenly developed acute pain in the right chest, accompanied by fever and chills. After being treated by her private

physician, a chest roentgenogram was taken and she was told she had pneumonia and pleural fluid. On July 31, 1946, she gave birth to her third child. The delivery was uneventful and she went home in the usual time.

She felt well until October 1946, when she again had pain in the right chest, accompanied by cough and loss of weight. At this time also she noted a sudden expectoration of a large quantity of thin, watery sputum. Because of these complaints, she was referred to the outpatient clinic of Pawling Sanatorium. As the findings were suggestive of pulmonary tuberculosis (figure 1), admission for observation was arranged on November 7, 1946, approximately four months after the onset of her symptoms.

Physical examination on admission showed a 29 year old woman who was 5 feet 4 inches in height and weighed 114 pounds. Her usual weight had been 125 lbs. She appeared to be a normally nourished and developed white woman, except for extreme pallor, and the abnormal physical findings were confined to the lungs. There was bronchial type breathing over the right upper lobe, with increased whispered and spoken voice. Over the lower half of the right lung, there was flatness on percussion and breath sounds were absent. Posteriorly and anteriorly over the mid portion of the right lung, there were numerous fine rales, with egophony at the level of the fifth dorsal vertebra posteriorly. The breath sounds on the left were exaggerated, with a bronchial quality in the upper lobe, but no rales were heard. The heart was not displaced, was regular, and no murmurs were heard. The blood pressure in mm. of mercury was 104 systolic and 78 diastolic. Laryngeal examination was entirely negative.

A serologic test for syphilis (Wassermann) was negative. The erythrocyte count was 5,020,000 and the total leukocytes 12,300 per cu. mm. with a normal differential. The concentration of hemoglobin was 84 per cent (Sahli). The urinalysis was normal. Several sputum examinations were performed which were negative, but on December 16, 1946, a 72 hour concentration test was reported positive for acid-fast bacilli. Subsequently, monthly sputum examinations from January to July, 1947, were all reported as negative, except on February 12, 1947, when a few acid-fast bacilli were again reported, although cultures of the specimen were negative for tubercle bacilli.

The patient was kept on the usual sanatorium regimen but, because serial roentgenograms failed to show improvement and because of the bilateral dissemination of the disease process, pneumoperitoneum was instituted on January 16, 1947. A satisfactorily uniform pneumoperitoneum (figure 2) was maintained by weekly refills of air, during which time she demonstrated clinical improvement with gain in weight and normal temperature, although the physical findings were in no way affected.

On March 17, 1947, there developed an acute pneumonic exacerbation in the right lung, which responded to penicillin. There was a recurrence of this early in May, and a chest film of May 6, 1947, showed a progressive involvement of each lung (figure 3).

She was considered to have an unusual type of pulmonary tuberculosis, for which streptomycin was advised. Before deciding to undergo this treatment, she took a leave of absence from the sanatorium, without approval. She returned on July 11, 1947, exhibiting a deterioration of her physical condition, with increasing dyspnea, loss of weight, and increase of pulmonary findings, both clinically and by roentgenogram. The pneumoperitoneum was not maintained during her absence from the sanatorium and the air was allowed to absorb.

On July 14, 1947, she was started on 1.0 Gm. of streptomycin daily. Treatment, totaling 128 Gm., was continued without inhibiting the progress of the disease (figure 4). The only toxic manifestation was a slight dizziness. Increasing dyspnea and cyanosis required continuous administration of oxygen from August 20, 1947, until death on October 30, 1947.

Necropsy Findings of Pleural Cavities and Lungs

Pleural cavities: The right pleural cavity contained 50 cc. of cloudy pink fluid. The surfaces of the anterior part were smooth and glistening. The lateral and posterior right pleural space was obliterated by heavy fibroid adhesive webs which bound the lung to the chest wall. The right lung filled approximately one-third of the pleural space.

The left anterolateral pleural surfaces were smooth, pink, and glistening. There were several heavy fibroid bands, but most of the lung was free from adhesions. The left pleural space contained 250 cc. of cloudy pink fluid. The left lung filled approximately one-half the pleural space.

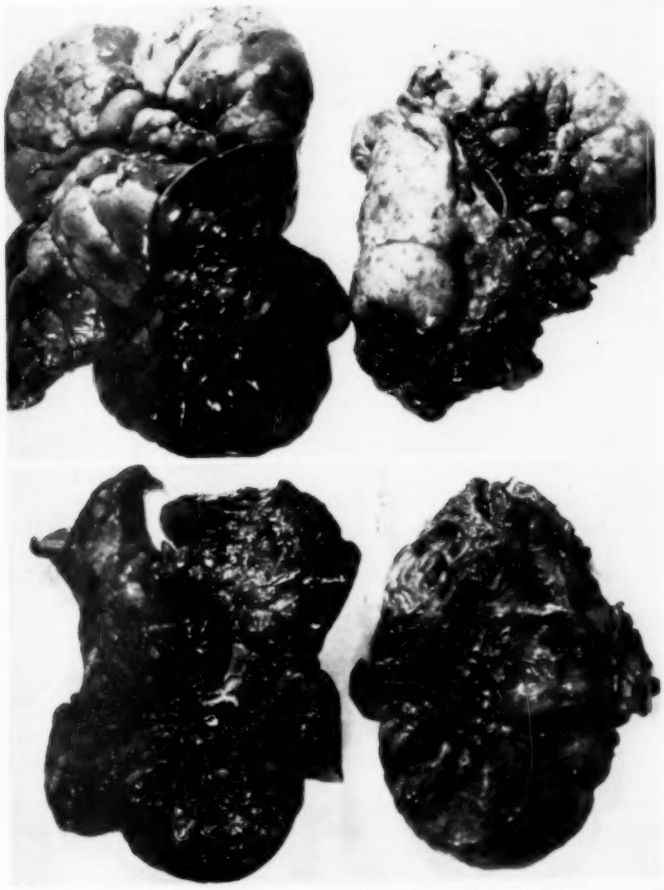

FIG. 5. (Top) Lungs showing contraction with distortion. There is marked chronic pleuritis of the lower lobe of the right lung.

FIG. 6. (Bottom) Cut surfaces of right and left lungs.

Lungs (figure 5): The right lung weighed 560 Gm. and the left 850 Gm. Both lungs were very irregular in contour and were markedly distorted. The surfaces were composed of nodular masses of reddish tissue which, on cutting, exhibited a finely granular, glistening surface. The middle lobe of the right lung was almost entirely replaced by this tissue and the lateral aspect of the lower lobe (right) was composed of granular, grayish-pink tissue which tore easily.

The cut surfaces (figure 6) were finely granular, firm and grayish-pink. The upper and lower lobes of the right lung and the upper and lower portions of the left lung were composed of firm, pink, glistening, moist lung tissue. Crepitation was present in these areas but was diminished.

The chief bronchial branches of each lung were encased in the grayish-pink tissue and their lumina were almost completely constricted.

The large pulmonary vessels were patent.

Microscopic Description

Lungs: In one section the pleura was thickened by heavy fibrous tissue heavily infiltrated by collections of lymphocytes. Each and every section of lung tissue showed the presence of large and small collections of atypical but quite well differentiated columnar epithelial cells (figures 7A and B). In places the cells appeared to be lining lung acini. The cells showed a tendency to form polypoid or papillary projections which protruded into the lumina of the alveoli. In some places the normal lung architecture was lost and the alveolar walls were

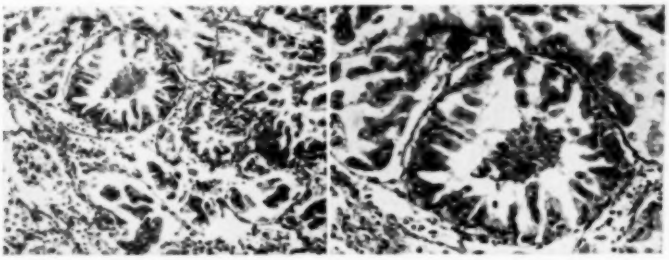

FIG. 7A. (Left) Low power field showing the presence of large and small collections of atypical but quite well differentiated columnar epithelial cells, which appear to be lining lung acini. The cells show a tendency to form polypoid or papillary projections, which protrude into the lumen of the alveoli.

FIG. 7B. (Right) High power field showing more detail.

replaced by large masses of atypical cells which showed a tendency to form papillary projections. In some situations, apparently the sites of oldest growth, there was fibroblastic activity and the tumor cells were supported by fibrous tissue. Sections from the hila of the lungs showed large amounts of neoplastic tissue. In no instance could the origin of the tumor cells be traced to bronchial mucosa. Mitoses were occasionally seen. Blood vessel invasion was not noted.

In general the pulmonary alveoli were dilated and contained large numbers of mononuclear phagocytes, but no polymorphonuclear leukocytes were seen.

DISCUSSION

From a clinical viewpoint, the lack of specific diagnostic criteria renders an accurate diagnosis of pulmonary adenomatosis very difficult. The roentgenographic findings *per se* present several problems in differential diagnosis. As contrasted with a solitary pulmonary tumor, multiple tumors, associated with the concurrent inflammatory changes, produce roentgenographic findings more characteristic of pulmonary tuberculosis than of neoplastic disease. The absence of tubercle bacilli, however, in view of the usual widespread roentgenographic findings, should lead one to suspect neoplastic disease. In addition, several of the cases reported presented the complaint of expectoration of large

quantities of thin mucoid sputum. Distant lymph node involvement by metastasis is almost always absent in pulmonary adenomatosis, so that biopsy for diagnostic purposes is precluded.

From the pathological viewpoint, the important consideration is the origin of the neoplasm, together with its proper classification. If this neoplasm arises from the bronchiolar mucosa, then the classification of terminal bronchiolar carcinoma is justifiable. Until the definite focus of origin is thoroughly established, pulmonary adenomatosis might be regarded as a distinct clinical and pathological entity.

CONCLUSIONS

1. A case of pulmonary adenomatosis in man is reported.
2. Diagnostic criteria are considered.
3. Pathological classification of this neoplasm is not yet completely established.

Acknowledgement

Gratitude is hereby expressed to Dr. Gustavus H. Klinck, Jr., formerly pathologist at Samaritan Hospital, Troy, New York, for the necropsy report and his assistance in prearing the illustrations.

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EDITORIAL

Integration of Streptomycin with other Forms of Therapy for Pulmonary Tuberculosis

When streptomycin became available for extensive clinical investigation in pulmonary tuberculosis, the principal problem was to determine its therapeutic value in various forms of the disease. At the same time important collateral information was sought regarding toxicity and the emergence of streptomycin-resistant strains of the tubercle bacillus in treated patients. To these ends the original investigators limited their therapeutic efforts to the use of streptomycin and bed rest alone in the treatment of their earlier patients. It quickly became apparent to experienced phthisiologists that streptomycin exerts a favorable influence in pulmonary tuberculous lesions having a fresh exudative component. Many investigators, working cooperatively, have also demonstrated a marked therapeutic effect in ulcerative mucosal lesions of the respiratory tract, in disseminated nodular pulmonary lesions (whether acute, subacute, or chronic), and in miliary tuberculosis. Although toxic drug reactions were frequent in the original patients studied, these became a lesser problem after reduction in the daily dosage.

It soon became apparent, however, that even in the carefully selected early patients, relapse of disease was frequent and that streptomycin alone in addition to bed rest was not a definitive cure for tuberculosis in the majority of patients. As surmised by Hinshaw and others, streptomycin exerts only a temporary, albeit powerful, suppressive effect against the tuberculous process. The action of the drug is limited to the period of time during which the tubercle bacillus remains sensitive to it. If this time is sufficient, the patient's inherent resistance mechanisms may become dominant and effect a natural remission of disease following streptomycin treatment. If predominance of drug-resistant bacilli occurs early, the patient usually reverts to his pretreatment status. If he is still unable to cope with his disease by his own defenses, the result is further progression of the disease unchecked by additional streptomycin.

Because of technical problems, direct application of laboratory data on streptomycin resistance of the tubercle bacillus to the clinical problems confronting the physician must be made cautiously. Nevertheless, considerable evidence has been accumulated by various investigators which permits one to assume that *in vitro* resistance is tantamount to *in vivo* resistance in the great majority of patients whose organisms have developed resistance to 100 to 1,000 γ of streptomycin per cc. of medium. This conclusion is based principally upon: (*1*) clinical and roentgenological relapse of patients during treatment simultaneously with the emergence of resistant tubercle bacilli in the sputum; (*2*) the failure of response after re-treatment with streptomycin among patients whose bacilli are known to be resistant as a result of a previous course of streptomycin. Once streptomycin-resistant strains of tubercle bacilli appear, they persist for months or years and may remain predominant indefinitely in a particular infection.

In various groups of patients, the incidence of emergence to predominance of highly resistant strains of tubercle bacilli may vary from 30 to 75 per cent in a given group. Upon analysis of the case material, this seeming discrepancy may be partially explained. In the early experience at the Laurel Heights Sanatorium, we were impressed with the high incidence of resistant organisms emerging in patients with gross caseation and cavity formation as contrasted with a group of patients with certain types of active, but relatively indolent, pulmonary disease without frank caseation or cavity formation. Similar relationships have been noted by others such as Woodruff, Riggins, Mitchell, and their associates. Obviously other factors do influence the emergence of resistant tubercle bacilli but at the present time it seems safe to assume, for practical purposes, that at least 60 per cent of the patients having gross caseation or cavitation will develop highly resistant strains of tubercle bacilli if treated by streptomycin and bed rest alone for a sufficient period of time. This seems true regardless of alterations in the dose regimen employed. Certainly the general experience has been that a reduction of the duration of treatment to 42 days from 120 days has not completely solved the problem of resistance. Resistant strains may begin to emerge as early as the thirtieth treatment day but are most likely to occur after six to eight weeks of treatment. Thus, in patients likely to develop resistant organisms, we can be certain of only about six to eight weeks of benefit from the suppressive action of streptomycin.

The use of combined therapy, such as para-aminosalicylic acid and streptomycin, or the advent of new drugs may eventually solve the question of streptomycin resistance. At the present time, however, the phenomenon remains a major problem.

Secondary only to the problem of resistant organisms in streptomycin treatment of pulmonary tuberculosis is the high incidence of relapse of the patient's disease after treatment with streptomycin has been completed. Among a group of 88 of our patients observed twelve to twenty-seven months after completion of streptomycin therapy, a definite roentgenological and bacteriological relapse occurred in 62 per cent of those with frankly caseous or cavitary disease when treated by streptomycin and bed rest alone. If gross caseation and cavitation (as judged by chest roentgenograms) were not present before treatment, however, a quiescent or arrested status was achieved by 67 per cent of the patients. Over-all relapse rates among patients treated by streptomycin and bed rest alone have been reported by others to range from 30 to 60 per cent. It is obvious from these data that the patient with frankly caseous or cavernous disease, who has demonstrated poor response to bed rest alone, is unlikely to achieve sustained arrest of his tuberculosis by the mere addition of streptomycin to the rest regimen.

The majority of sanatorium patients in whom the use of streptomycin is most urgently needed have pulmonary disease of a mixed type of pathology. Usually the basic lesion is of a fibro-caseous-cavernous type with an additional component of a more exudative reversible type of disease. Occasionally the therapeutic problem is one of blocked or tension cavities, presumably the result of endo-

bronchial involvement in association with parenchymal disease. Perhaps our greatest therapeutic problem is the patient with active cavitary disease which is suitable for collapse, but should not be collapsed because of the presence of recently progressive contralateral disease. These various types of involvement comprise, in a large measure, the chief problems of the physician treating pulmonary tuberculosis. How may streptomycin be used most wisely in this large group of patients needing some additional aid to effect a natural remission of their disease?

It is in patients with the above categories of disease that the temporary suppressive action of streptomycin is most limited in duration by the frequent emergence to predominance of streptomycin-resistant strains before the patient's inherent resistance mechanisms become dominant. It is also in this type of disease that post-treatment relapse is most common. Thus it is incumbent upon the physician to evaluate carefully the potentialities of streptomycin and bed rest alone in a given case. Is he willing to sacrifice streptomycin sensitivity for a short duration of clinical and roentgenological improvement in a patient who is ill with a disease known to be of a chronic relapsing nature? Had he not better plan his therapeutic program on the basis of a six to eight week period of suppression of disease by streptomycin and, during this period, attempt to accomplish some more definitive form of treatment? All too many patients are entering sanatoriums who have had a prior course of streptomycin, experienced temporary clinical or roentgenological improvement, developed streptomycin-resistant infections, relapsed, and thus have lost the golden opportunity for collapse therapy once afforded them by streptomycin.

In a majority of patients with disease of a purely disseminated character without cavitation, the addition of streptomycin alone to the usual bed rest regimen will often be sufficient to reverse an unfavorable trend and permit the patient to achieve true arrest of his disease. Response is usually equally satisfactory and relapse rate is low in patients treated promptly for fresh exudative noncavitary lesions. Moreover, the emergence to predominance of drug-resistant strains of tubercle bacilli are less likely to be encountered following treatment of such patients.

The great majority of patients in whom the use of streptomycin is contemplated should have a careful over-all appraisal of their disease. This requires prior consultation between the physician and the thoracic surgeon. A complete plan of treatment should be outlined predicated upon: (*1*) the known suppressive action of streptomycin against the more responsive types of pulmonary tuberculosis; and (*2*) the known effective collapse measures in cavitary or caseous disease.

If the patient's disease is of a sufficiently destructive nature to warrant thoracoplasty or resection, yet his poor clinical condition or active contralateral disease precludes such an immediate procedure, streptomycin may prove an invaluable agent in bringing him to major surgery. Once the objective, thoracoplasty or resection, has been decided upon all concerned should adhere strictly to the therapeutic plan. With initial symptomatic, bacteriologic, and

roentgenologic improvement frequent in the majority of well selected patients receiving streptomycin, the physician, as well as the patient, may feel that major surgery may be avoided. This hope may be fulfilled in a minority of patients but at present we cannot predict which patient will fall into this fortunate group. All too frequently the patient relapses during treatment, has developed streptomycin-resistant tuberculosis, and is unresponsive to further therapy with this agent. Likewise, the conservative surgeon must be convinced that once a favorable trend has become manifest, usually after three to four weeks of streptomycin treatment, he may perform the thoracoplasty or resection with a fair degree of safety, even though there has recently been active or progressive disease in the same or opposite lung. Experience in this and other clinics (Levine, Klein, Froman) has demonstrated that such a procedure is practicable and reasonably safe. One need not wait for a definite favorable roentgenological change in the relatively good lung. If an initial favorable clinical response is noted and the minor lesion in the better lung is of the type of noncavitary disease known to be responsive to streptomycin, one should proceed immediately with surgery while still enjoying the benefits of streptomycin.

If the initial response to streptomycin proves disappointing and major surgery still seems contraindicated after about six weeks of treatment, it may be well to attempt a minor collapse procedure such as phrenic-pneumoperitoneum. This may eventually result in sufficient stabilization of the patient's disease to permit major surgery at a later date. In such a patient it would seem prudent to discontinue streptomycin on the assumption that a high proportion of the remaining bacilli are drug-resistant. Even if this has not occurred, however, it is advisable to discontinue chemotherapy in order to save the remaining period of suppressive action of the drug for use at some later date.

In other patients, over-all assessment of the problem may result in a decision to use pneumothorax or phrenic-pneumoperitoneum as a definitive treatment. If this be the case, one should integrate the selected procedure promptly in order to receive maximum benefit from the combination of streptomycin and collapse. Obviously, not all patients require streptomycin in conjunction with these procedures but in the acutely and severely ill patient the usual "cooling off" period before collapse measures are instituted may be shortened by its use. In our limited experience, however, pleural complications have not been avoided by a preliminary course of streptomycin before collapsing the acute lesion.

Favorable response of visible endobronchial tuberculosis suggests the use of streptomycin in conjunction with pneumothorax for the treatment of tension cavities. Results to date in a limited number of patients have been disappointing but the problem is worthy of further investigation.

In a large series of patients who were "standard risk" thoracoplasty candidates, the routine use of streptomycin as a prophylactic measure in the Veterans Administration produced but a very slight lowering of complications in the treated patients when compared with alternate controls. It would seem more intelligent to reserve streptomycin for the treatment of complications when they occur.

In the standard resection candidate, especially with tuberculous endobron-

chial disease, the use of streptomycin prior to, and for a few weeks following, the operation may be beneficial in lessening immediate postoperative complications. There is no evidence as yet that such treatment will affect the major problem of long term relapses.

The present tendency to give a course of streptomycin and see what it will do is to be deplored. Each patient should be carefully appraised and an over-all plan of treatment be outlined based upon close integration of the temporary suppressive action of streptomycin with known effective collapse procedures. Once decided upon, the plan should be followed to its predetermined objective despite a temporary improvement with streptomycin alone. In this manner we will have: (*1*) fewer patients obtaining only temporary improvement at the price of developing drug-resistant tuberculosis; (*2*) more patients obtaining maximum benefit from streptomycin therapy, simultaneous control of their disease by collapse treatment, and a better chance for permanent arrest of their disease.

Until a new agent effective against streptomycin-resistant strains of the tubercle bacillus becomes available, or until we can delay the emergence of resistant strains by the simultaneous administrations of two or more drugs, we should use the temporary opportunity frequently presented by streptomycin to accomplish during that period all we can toward a definitive cure of the patient. Thus it seems wise to heed the advice of Horace, "Seize now and here the hour that is, nor trust some later day."[1]

JOHN B. O'CONNOR

[1] "Carpe diem, quam minimum credula postero." Ode XI, Leuconoe.

LETTERS TO THE EDITORS

A PYRIDINE DERIVATIVE AND EXPERIMENTAL TUBERCULOSIS

To the Editors of the American Review of Tuberculosis:

Antibiotic action in tuberculosis reached a new height with the advent of streptomycin and dihydrostreptomycin, yet there are many phases of the action of these substances *in vivo* which are not clearly defined nor understood today in the simple sense of a direct chemotherapy. Their peculiar localized effects *in vivo* on tuberculosis, their inability to destroy tubercle bacilli in relatively high concentrations *in vitro* as well as *in vivo*, the fact that the tubercle bacilli can develop a resistance toward high concentrations *in vitro* and *in vivo* in a relatively short time, and that the persistence of the effects *in vivo* are not dependent upon adequate concentrations of the antibiotic are intriguing. Such information warrants further studies to disclose the mechanism of chemotherapy in the hope of overcoming some of the inadequacies in treating tuberculosis with these agents.

Recently a highly potent *in vitro* static pyridine was described in the form of 2 butoxy-5 amino pyridine sodium formaldehyde bisulfite (ABF) which apparently lacked action *in vivo*, as deduced from inconclusive feeding experiments (Harry W. Feinstone, Proc. Soc. Exper. Biol. & Med., 1946, *63*, 153; Duca et al., Proc. Soc. Exper. Biol. & Med., 1948, *67*, 159). The treatment was begun a week after heavy subcutaneous infection and consisted of two incompletely spaced injections on the basis of blood analyses, and in amounts producing local ulcers. The lack of adequate explanatory experiments made it appear advisable to pursue further studies with it. Accordingly, it was found that the medium played an important part in the results with $\alpha\alpha$ diaminopyridine monohydrochloride (PDM). The action of this pyridine resembles streptomycin and dihydrostreptomycin which, even under standard planting of acid-fast saprophyte (Day) and human tubercle bacilli as test organism, varies in different mediums. However, this variable effect on nutrients was not so great in the case of ABF. The greater stability of ABF in *in vitro* action in a range of different mediums was further noted in the nearly equivalent effects upon the acid-fast saprophyte (Day) and the human tubercle bacilli. In relatively high concentrations, 10 mg. per cc., which is about 1,000 times the retarding concentration, contained in a nonprotein simple nutrient medium (Wong-Weinzirl), ABF destroys the viability of the acid-fast saprophyte Day in about three to six days at 37° C. Concentrations below 10 mg. per cc. (0.1 mg. per cc. in over four days) require much longer exposure to destroy the viability of these acid-fast bacilli. ABF is a more efficient tuberculocide than streptomycin. On human tubercle bacilli, ABF acts about the same as on the acid-fast saprophyte, although its potency appears to be slightly greater in that viability is destroyed by 1.0 mg. per cc. concentration within six to ten days and 0.1 mg. per cc. succeeds within twenty to forty days. It appears also to be a more potent retardant of the growth of human tubercle bacilli *in vitro* in simple nutrient mediums than streptomycin. In order to test the neutralizing effect of tissues upon ABF, various amounts were mixed with one gram of ground guinea pig tissues, and growth inhibition was tested against the acid-fast saprophyte Day planted in concentrations of 0.02 mg. of suspension per cc. The findings indicated that ground liver and kidney tissues could neutralize the retarding action of more than 0.01 mg. of ABF, whereas the retarding action remains at about 0.001 mg. for lung, spleen, brain, and blood. This neutralizing effect was also noted for ground liver tissue against streptomycin when one gram of tissue abolished the effect of 50 units (50

γ) of streptomycin (Corper, H. J., and Cohn, M. L., Yale J. Biol. & Med., 1946, *19*, 1; Corper, H. J., and Cohn, M. L., J. A. M. A., 1948, *137*, 357).

Following the intravenous (or subcutaneous) injection of relatively large amounts (135 mg.) of ABF, the retardant effect persisted for only a comparatively short period of time (never exceeding six hours). After oral administration, it was not discernible.

In view of the fact that ABF showed a definite and constant *in vitro* retarding effect upon the growth of the acid-fast saprophyte Day and the human tubercle bacilli in simple nutrient mediums, and that its retarding effect was discernible also in the blood and certain tissues following its injection subcutaneously, it appeared advisable to follow these effects by treatment experiments in guinea pigs. For this purpose we used the decisive intravenous (ear vein) infection method of giving virulent tubercle bacilli in fine suspension to guinea pigs (Corper, H. J., and Cohn, M. L., J. A. M. A., 1945, *127*, 1043).

The results of this treatment study with ABF in intravenously infected guinea pigs indicate that ABF given in a single daily amount of 20 mg. subcutaneously was without appreciable effect upon either the tuberculous lesions or the fatal issue produced by the intravenous injection of one milligram of virulent human tubercle bacilli. In order to further correlate treatment with the persistence of the ABF action in the blood, the repeated administration of 20 mg. at two-hour intervals subcutaneously was tried (total daily dose, 240 mg.). These intensive treatments with ABF also proved to be without effect on the tuberculosis and appeared to hasten the lethal issue in the animals slightly. It is to be noted also from these studies that the ABF was without appreciable effect on spleen size in the treated animals except for the intensive treatment series where a perceptible but not marked splenomegaly resulted. This study likewise revealed that the ABF treatment was without beneficial or detrimental effect upon the results obtained with streptomycin used coincidently in 25,000 unit amounts daily. However, in spite of the long combined treatment period and evident absence of marked gross tuberculosis in these animals, cultures of tubercle bacilli were obtained from all the important organs in these animals and the strains of tubercle bacilli isolated from these animals proved streptomycin-resistant.

A similar treatment experiment was performed with guinea pigs using phenyl azo α α diaminopyridine monohydrochloride, PDM, as therapeutic agent given both by subcutaneous injection and orally in pure powder form in No. 5 gelatine capsules to a total of 100 mg. per day. The presence of PDM in the blood and urine could be recognized easily by its color, and its presence was determined by the retarding effect on the growth of the acid-fast saprophyte "Day."

PDM is without appreciable effect upon the tuberculosis resulting from the intravenous injection of 1.0 mg. of fine suspension of virulent human tubercle bacilli (*s* 4008) even when given in amounts imparting a decided yellow color to the tissues in general. The PDM was also without effect on the lethal issue resulting from the intravenous injection of the human tubercle bacilli. When given in large amounts orally, this effect was hastened.

It appears from the foregoing studies with PDM that, even though a chemical agent is a good retardant to the growth of acid-fast saprophytes and tubercle bacilli in a relatively poor nutrient medium and its presence is indicated in sufficient amount for similar retardation of the growth of tubercle bacilli, such retardation of the tubercle bacilli *in vivo* or of the disease tuberculosis does not occur. This is probably because the complex colloidal nature of the body fluids and tissues precludes such action, which would appear to be suggested by the facts that the guinea pig is naturally highly susceptible to infection with virulent mammalian tubercle bacilli and that the retardant effect noted for relatively

poor nutrient mediums is almost completely negated when the PDM is incorporated in a good nutrient medium such as the egg yolk. And this is in spite of the evident fact that the PDM appears to be present sufficiently in the free state to retard in amounts acting in a poor nutrient.

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THE AMERICAN REVIEW OF TUBERCULOSIS
ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Tuberculous Pleural Effusion.—Tuberculous pleural effusion is rare in childhood. One-half of the cases are seen between the ages of 15 and 25. About 25 per cent develop pulmonary tuberculosis within five years; up to 10 per cent succumb. A total of 149 cases were seen by the author. They were divided according to age as follows: early school (5 tc 8 years), 18 cases; late school (9 to 13 years), 37 cases; early adolescence (14 to 15 years), 36 cases; and adults (16 years and over), 58 cases. There was a predominance of males in all groups, greatest in the younger and decreasing with advancing age. Likewise, the incidence of a history of family contacts decreased with advancing age. Only one patient had erythema nodosum. The tuberculin test was positive in 84 of the 91 children; in the other 7 it was not done, as tuberculosis was proved by other means. The sputum showed tubercle bacilli in 2 children and 3 adults. There was a lower percentage of gross effusions in children than in adults but 91 per cent of the youngest group showed hilar nodes as compared to 38 per cent of the older patients. In the youngest group, no pulmonary infiltrations were seen; the incidence rose to 24 per cent in the adult group. No calcifications were seen in the children's roentgenograms. Other tuberculous involvements, such as bone and joints and cervical and abdominal lymph nodes, were very infrequent and were equally divided between children and adults. All the patients were given general sanatorium care. During a follow-up of four years or more, none of the children in the two younger groups, 5.5 per cent of the early adolescents, and 11 per cent of the adults developed pulmonary tuberculosis.—*A study of tuberculous pleural effusion in children and adults, N. Landau, Tubercle, February,* 1949, *30: 26.*—(*A. G. Cohen*)

Primary Complex and Bronchoscopy.—Bronchoscopy has greatly elucidated the pulmonary manifestations which follow the primary tuberculous infection. In uncomplicated primary infections, the orifice of the bronchus to the lobe where the primary focus is located usually is slightly congested and edematous, showing a mucous secretion rich in polymorphs and macrophagocytes. In cases of chronic epituberculosis, edema of the main bronchus of the diseased lobe is predominant and the narrow central opening may be obstructed by a plug of tightly packed macrophagocytes. The bronchial glands perforate and form fistulas much more frequently than was presumed. These small fistulas may be single or multiple and form simultaneously or successively. Their presence is suggested by paroxysmal cough, a "stitch in the side," temperature, and transient expectoration of sputum containing tubercle bacilli. Many of these minute fistulas soon stop discharging and close within a few months. Some openings obliterate; others remain visible as scars. Glandular dissemination may leave multiple calcifications in the lung field concerned. Bronchiectasis may form subsequent to chronic epituberculosis, atelectasis, calcified hilar glands, and fibrosis.—*Étude bronchoscopique et comportement des bronches au*

cours des périodes primaire et secondaire de l'infection tuberculeuse, A. Dufourt & P. Mounier-Kuhn, Schweiz. Ztschr. Tuberk., 1948, no. 2: 65.—(*E. Dunner*)

Endobronchial Tuberculosis.—As judged by bronchoscopic and roentgenographic observations, endobronchial tuberculous lesions began in the surrounding lung tissue in the majority of 20 patients. Emphasis is placed on the fine or coarse infiltrations seen in the pulmonary tissue in the immediate vicinity of the hilum. If a progressive pulmonary lesion exists simultaneously with the tuberculosis of a draining bronchus, the use of pneumothorax appears justified but it is to be avoided if an endobronchial lesion exists independently. —*Ein Beitrag zur Kenntnis und Therapie der Bronchustuberkulose, H. Rechenberg & A. Labhart, Schweiz. Ztschr. Tuberk., 1949, no. 1:* 29.—(*E. Dunner*)

Constrictive Pericarditis.—There are 3 forms of chronic pericardial disease: asymptomatic, constrictive (*concretio cordis*), and *accretio cordis*. In the asymptomatic type, the pericardial cavity is obliterated by fine adhesions. The parietal and visceral layers are not thickened or closely adherent. This type is seen in old myocardial infarction and in some unidentified diseases. In constrictive pericarditis the heart is normal or reduced in size. It is encased in a greatly thickened dense fibrous pericardium which is not adherent to the chest wall. The etiology is almost always tuberculosis. In *accretio cordis* the heart is enlarged; it is encased by a moderately thickened pericardium, the two layers of which are adherent and are attached to the chest wall. The etiology is almost always rheumatic fever. This article is concerned with constrictive pericarditis. In previously reported cases, there was no evidence of rheumatic fever, uremia, infarction or malignancy. Histological examination gave no clue as to the etiology. No patient gave a past history of pericarditis. To determine the etiology, the authors decided to trace the course of the disease which was the probable origin, namely acute tuberculous pericarditis. In its simple form, this is a fairly benign disease, often difficult to differentiate from constrictive pericarditis. The pericarditis frequently is part of the syndrome of polyserositis which is a more serious condition. In either type, it is difficult to find tubercle bacilli. The circulatory effects are like those of constrictive pericarditis; the venous pressure never falls to normal nor does the liver return to normal size. Of 18 cases of acute tuberculous pericarditis, including 4 without and 14 with tuberculosis of other serous cavities, 16 developed constrictive pericarditis. The heart shadows became smaller with less intense pulsations. Engorgement of neck veins and ascites were characteristic. Seven patients with polyserositis were not operated upon and all died of widespread tuberculosis in seven months to five and one-half years. In 9 cases, operation was performed. In all but one, active tuberculosis of the pericardium was encountered. Preoperatively, it could not be determined whether or not the tuberculous process had healed. There were 3 operative deaths. Of the other 6 patients, 2 developed tuberculosis elsewhere in the body. The risks of tuberculous spread are thought to be exaggerated. The policy is to delay operation as long as possible but not unduly long. Of 7 patients with acute septic pericarditis in the terminal stage of sepsis, 5 died and 2 recovered. Neither of the surviving patients developed constrictive pericarditis. The authors doubt the existence of acute idiopathic pericarditis.—*The aetiology of constrictive pericarditis, with specific reference to tuberculous pericarditis, together with a note on polyserositis, G. W. S. Andrews, G. W. Pickering & T. H. Sellors, Quart. J. Med., October, 1949, 17: 291.*—(*A. G. Cohen*)

Tuberculosis of Greater Trochanter.—Tuberculosis of the greater trochanter of the femur with involvement of the overlying bursa was found in about 0.2 per cent of cases of tuberculosis. The authors report 12 patients averaging 28 years of age, the youngest being 7 years old. It is thought that trauma was a causative factor in several

of the patients although many had tuberculosis in other locations. Usually the patients noticed a swelling over the trochanter or complained of pain over the outer aspect of the thigh. A fluctuant swelling usually was found extending backward over the buttock; a sinus was sometimes present. Movements of the thigh were unaffected but passive adduction often produced considerable pain. Roentgenograms showed erosion of the periphery of the greater trochanter or an encysted area in the middle of the trochanter. Drainage was instituted in 3 cases before the nature of the lesion was ascertained. None of the lesions healed and all were excised later. Aspiration in 3 cases was followed by sinus formation and excision was performed. Incision and curettage of the walls of the abcess were done in 5 cases with healing in 4, in 2 by primary intention. In 7 cases the bursa and the involved portion of the trochanter were excised. This was done also in one case of tuberculous osteomyelitis of the trochanter. In 2 of these cases there was healing by first intention; sinuses developed in 6, but all healed within seven months after the operation.—*Tuberculosis of the great trochanter, B. McMurray, Brit. M. J., September 27,* 1947, *no. 4525: 492.*—(*R. W. Clarke*)

Role of Pleura in Pneumonectomy.—With the removal of a tuberculous lung and its visceral pleura, the parietal pleura left *in situ* not only loses its function and usefulness but becomes a source of serious postoperative complications. Infection of the remaining pleura during or following pneumonectomy is not uncommon. Accordingly, the effect of total pleurectomy on the incidence of post-pneumonectomy complications, particularly empyema, was investigated. A review of 77 consecutive pneumonectomies showed that, following intrapleural pneumonectomy in 52 of these cases, bronchial fistula and/or empyema developed in 19. In addition, 8 patients had wound difficulties, 5 developed a bronchogenic spread, and 9 died. In contrast, following extrapleural pneumonectomy with removal of all or nearly all of the parietal pleura in 25 cases, a bronchial fistula developed in 2 and wound difficulty in one. There was no instance of empyema or spread and no death occurred. The extrapleural approach in these cases was selected for technical reasons, principally the presence of encapsulated empyema or pleural symphysis. The general care and technique were identical with that for intrapleural pneumonectomy, the only variation being the complete or practically complete removal of the parietal pleura at the time of pneumonectomy. It is possible that the future treatment of bronchopleural fistula and empyema will consist primarily of extensive pleurectomy followed, if necessary, by bronchoplasty and thoracoplasty. —*The role of the pleura in intra and extrapleural pneumonectomy: Follow-up of seventy-seven consecutive cases, I. G. Tchertkoff & I. A. Selikoff, Quart. Bull., Sea View Hosp., October, 1947, 9: 277.*—(*K. T. Bird*)

Early Intrapleural Pneumonolysis.—At the Tiuruniemi Sanatorium, Finland, during 1945 and 1946 the aim was to perform all intrapleural pneumonolyses within one month after the induction of pneumothorax. Some had to be postponed when there was an accumulation of cases. Of 174 cases during 1946, pneumonolysis was attempted in 74 per cent before the fortieth day. In 14 cases, the procedure was done within two weeks. A complete severance of adhesions was possible in 75 per cent of the cases when intrapleural pneumonolysis was performed within one to five weeks after the induction of pneumothorax, compared to 55 per cent when the procedure was delayed for two or more months. Early pneumonolysis did not result in more complications but, rather, reduced the total incidence of febrile effusions and of intrapleural bleeding. The length of the sanatorium stay was reduced also.—*Optimum time for intrapleural pneumonolysis, S. Anttila, Acta tuberc. Scandinav., 1947, 21: 274.*—(*K. T. Bird*)

Tuberculin Sensitization.—An attempt has been made to solve the ancient, controversial,

but important problem of whether tuberculin tests can produce a sensitivity to the substance in nontuberculous individuals. Eleven infants were found to be negative by Mantoux test to 1:100 dilution of O.T. They were then kept in isolation and Mantoux tests were repeated at about 48 hour intervals. From 11 to 60 tests were done on each infant during periods of one to six months; 2 individuals had small areas of erythema (on one and three occasions) with subsequent negative tests. Twelve infants were similarly tested with tuberculin patch tests. From 8 to 29 tests were done during periods of one to six months; 3 individuals had from one to three questionable reactions followed by repeated negative tests. It can be concluded that studies which require repeated tuberculin tests are safe from the hazard of lasting sensitivity from the tests.—*Nonsensitization to repeated tuberculin tests, J. Schwartzman, M. Schneider & M. E. Crusius, J. Pediat., December, 1948, 33: 746.*—(*W. H. Oatway, Jr*).

Complications of BCG Vaccination.—Vaccination with BCG by the subcutaneous route is known to be followed sometimes by the formation of nodules and fistulous abscesses which may last for several months and which heal in the manner of cold abscesses. Little has been published about the complications of BCG vaccination by Rosenthal's intradermal technique. In a few patients vaccinated intradermally, however, following types of reactions have been observed: (*1*) local reactions of minor consequence at the site of vaccination; (*2*) lymphadenopathy in the regional nodes of the vaccination site; (*3*) distant lymphadenopathy of the mediastinal, inguinal, or supraclavicular nodes. The local reactions consist of macules, papules, and single or multiple abscesses ranging in size from that of a millet seed to that of a small marble. These suppurate and heal with scarring. The regional reactions consist of the enlargement of one or more axillary lymph nodes which may reach the size of a pigeon's egg and contain more than 10 cc. of pus. They generally suppurate and form fistulas which run a chronic course, usually of several months' duration. When they heal, the scar has the classic scrofulous character. These lymph node enlargements appear at any time from fifteen days to eight months after vaccination and are not accompanied by any systemic reactions. The pus obtained from the lesions is like that of a cold abscess and in some cases may contain acid-fast bacilli. In most cases, none can be found. In 2 of the 12 cases cited by the authors, mediastinal, inguinal, and supraclavicular lymph node enlargements occurred. The mediastinal enlargement was easily demonstrated in the chest roentgenogram.—*Las complicaciones ganglionares supuradas de la vacunación BCG Rosenthal, P. Cantonnet Blanch, H. Cantonnet Blanch, and A. Pérez Scremini, Rev. de tuberc. d. Uruguay, June, 1948.* **16**: *85.*—(*F. Pérez-Pina*)

Tuberculosis and Sarcoidosis.—In discussions about the correlation between sarcoidosis and tuberculosis, cases have been cited in which the sarcoid manifestations are said to have regressed markedly during the development of chronic tuberculosis. Critical study of the literature shows that only a few cases of this nature have been observed and regression of the cutaneous sarcoid lesions during the development of tuberculosis is not the rule. A woman with extensive sarcoid lesions of the skin and osseous system was followed for five years. No regression of the sarcoid lesions was observed although she had gradually progressive, bacillary, cavernous, pulmonary tuberculosis with associated tuberculous spondylitis and probable tuberculosis of the knee during this time. The coexistence of these manifestations of typical sarcoidosis and typical tuberculosis during this long period suggests that these are two separate diseases.—*Progressive Boeck's sarcoid associated with protracted destructive tuberculosis, R. Th. Bjørnstad, Acta tuberc. scandinav., 1948, 22: 142.*—(*K. T. Bird*)

Clinical Studies, Nontuberculous Diseases

Pulmonary Eosinophilosis.—Pulmonary eosinophilosis is a clinical condition char-

acterized chiefly by cough, paroxysms of dyspnea, and elevation of the white blood count with relative and absolute eosinophilia. Frequent systemic manifestations are fever, loss of weight, and lassitude. The literature contains 685 cases answering this description which were reported under many different titles. Most were reported from India and Ceylon and a few from other countries. All ages from one to 62 years were represented with the highest incidence from 20 to 40 years. There was a preponderance among males but the occupation of the patient was irrelevant. Mites were found in the sputum of some; there is some question as to the etiological significance of this finding. There were no autopsies. Clinically, there are 2 types: acute and chronic. The acute type begins abruptly with fever and cough as in pneumonia. The signs are those of bronchitis, with or without consolidation. In 25 per cent, the chest becomes clear in four to six weeks. The remainder enter the chronic phase. The chronic type, which is more frequent, either begins insidiously or is a residual of the acute type. It lasts for months or years with remissions or exacerbations. At first there is a nonproductive cough and mild fever; after one month, scanty expectoration appears. Later there is breathlessness and, less often, expiratory dyspnea. The fever lasts one to two months and the respiratory symptoms one year or more. The sputum often contains eosinophils. The spleen is enlarged in 50 per cent. The total white blood count ranges from 12 to 80 thousand with 20 to 80 per cent eosinophils. There is a high titer of cold agglutinins and a positive Wassermann or Kahn test is obtained in some. Roentgenograms show disseminated mottled shadows throughout all or parts of the lungs; later only increased markings remain. The differential diagnosis includes helminthiasis, asthma, and Löffler's syndrome. In asthma the white blood count is rarely elevated, roentgenograms are negative, and arsenicals give no relief. Löffler's syndrome is much milder and shows no constitutional symptoms. Arsenicals are specific therapy for pulmonary eosinophilosis; less than 2 per cent fail to respond. The treatment consists of eight weekly injections of 0.15 to 0.30 Gm. of neoarsphenamine. The author reports 207 cases, of which 11 were acute and 186 were chronic, with an abrupt onset in 22. Smears and cultures of the sputum were negative but mites were found in 21 cases. This finding was considered to be incidental, the balance of evidence favoring infection as the etiology. The Wassermann test was positive in 65 cases (32 per cent). The eosinophilia fell as treatment was given but improvement in other respects was more rapid. The first injection of the arsenical often caused an increase in eosinophils and an exacerbation of symptoms. —*Pulmonary eosinophilosis, V. Wiswanathan, Quart. J. Med., October, 1948, 17: 257.*—(*A. G. Cohen*)

Histoplasmosis.—About 100 cases of histoplasmosis have been reported; this report adds 10 cases from the Kansas City area. Five cases were fatal; 2 apparently have recovered. Seven patients were sensitive to a skin test with histoplasmin and 7 showed positive complement fixation reactions. Pulmonary infiltrations were noted in 9 of the cases, in 2 of which the lesions were of a miliary type. In 2 cases coexistent tuberculosis was demonstrated. A third case had Hodgkin's disease, proved post mortem by microscopic and cultural examination to be complicated by histoplasmosis. It is of interest that *Histoplasma capsulatum* was isolated by culture from the gastric contents of 4 patients.—*A report of ten proved cases of histoplasmosis, I. Bunnell, M. Furcolow, Pub. Health Rep., March 5, 1948, 63: 299.*—(*S. Hadley*)

Honeycomb Lungs.—A variety of cystic disease of the lungs is described in which thin-walled cysts up to 1.0 cm. in diameter are distributed uniformly throughout the substance of both lungs. Sixteen cases were seen, of which 6 had systemic disease. The outstanding clinical features were spontaneous pneumothorax, often bilateral, and right heart failure. One case had xanthomatosis as did 3 of those reported in the literature. Pulmonary xanthomatosis is not rare. If

healing occurs, the lipoid cells are replaced by diffuse interstitial fibrosis and, in a few, cystic disease results. Biliary cirrhosis was seen in 2 cases. Tuberous sclerosis was noted twice; about 10 cases were found in the literature. There were 2 cases with pituitary disorders. The remaining 10 cases had no systemic disease. The age at onset ranged from 7 to 55 years; the time from onset to death was one to six years. The patients were mostly males. Spontaneous pneumothorax occurred in 8 cases, and was bilateral in 5 of them. In 8 there was progressive dyspnea; 4 died of cor pulmonale within two years. Radiographically, there was a fine to coarse reticular pattern. The cystic spaces were more conspicuous when a pneumothorax was present. Tomograms in 4 cases demonstrated the honeycombing. Bronchography was done in 4 cases; the iodized oil did not enter the cysts. Histologically, there was interstitial fibrosis with no evidence as to cause. The cystic changes very likely are secondary to mechanical factors in acquired disease. The underlying disease is probably inflammatory, though this is not proved.—*Honeycomb lungs, N. Oswald & T. Parkinson, Quart, J. Med., January, 1949, 18: 1.*—(*A. G. Cohen*)

Pulmonary Embolism.—Pulmonary embolism, but not thrombosis, rarely occurs in children; 29 cases have been reported as occurring at ages less than fifteen years. The case of a boy who died suddenly at the age of nine years is reported. He had recovered from two episodes of pulmonary illness during the previous seven and one-half months during which time he had also had transient symptoms in the abdomen, one inguinal area, and both legs. Autopsy showed a massive new pulmonary embolism, signs of an older minor embolus and infarct, and partially organized thrombi in the inferior vena cava and common iliac veins. The rarity of peripheral thrombophlebitis in children is emphasized.—*Pulmonary embolism in childhood, G. F. Stevenson & F. L. Stevenson, J. Pediat., January, 1949, 34: 62.*—(*W. H. Oatway, Jr.*)

Sarcoidosis.—The authors have used calciferol and dihydrotachysterol 50,000 to 300,000 units daily. Patients with sarcoidosis do not tolerate calciferol as well as patients with lupus vulgaris, and the more extensive the disease, the more severe are reactions. Early toxic symptoms consist of anorexia, nausea and vomiting, malaise, weakness, and dizziness. Dihydrotachysterol has been used in a dosage of 3.75 mg. daily for three days to be followed by 1.25 or 0.625 mg. daily for several months. Dihydrotachysterol is tolerated much better than calciferol, but eventually may give rise to the same symptoms.—*Sarcoidosis: III. A review, A. C. Curtis & R. H. Grekin, M. Clin. North America, January, 1949, 31.*—(*B. Hyde*)

Primary Pneumonitis.—A five months old baby became ill with sneezing, cough, and fretfulness as the main symptoms. Both parents had a mild upper respiratory infection several days prior to the onset of the baby's illness. The baby recovered after being febrile for several days. Pharyngeal smears from the patient and from both parents showed characteristic cytoplasmic inclusion bodies. Subsequent smears made from the patient and from the father showed a decreasing incidence of cells with inclusions during a period of ten days.—*Primary pneumonitis in infancy, J. M. Adams, J. A. M. A., December 18, 1948, 138: 1142.*—(*H. Abeles*)

Dual Fungous Infection.—The case of an eight year old boy who had a fatal infection with two fungi is presented. The child had pneumonia twice before the age of two years, a ringworm-like skin involvement of four years' duration from which *Candida albicans* was cultured after an exacerbation, and 4 pneumonic attacks in the fourteen months prior to hospitalization. Roentgenograms then showed soft nodular densities extending out from the hilar regions, much larger on the right. The sputum was positive for the same fungus. Skin test by an autogenous antigen was mildly positive; desensitization attempts

were followed by a clinical exacerbation. The urine culture was positive. Meningitis supervened and both *Candida albicans* and *Cryptococcus neoformans* were found in the spinal fluid and urine for 48 hours before death. Necropsy showed a generalized dissemination of the infection with cultures of various tissues irregularly positive for the two organisms.—*Candida albicans and Cryptococcus neoformans occurring as infective agents in an eight-year-old boy, C. Spicer, W. O. Hiatt, & J. F. Kessel, J. Pediat., December, 1948, 33: 761.*—(*W. H. Oatway, Jr.*)

Histopathology of Bronchiectasis.—Fifty human lungs that had been resected at the Mayo Clinic because of bronchiectasis were carefully sectioned, examined microscopically, and compared with sections of tissues from animals suffering from Jagziekte and chronic progressive pneumonia. In bronchiectasis the pulmonary alveoli commonly had a visible continuous lining of cells. These cells were derived from bronchial epithelial cells or from the pericapillary cells of the alveolar wall. The latter origin was far more frequently encountered than was the former. The appearance of the cells of alveolar origin differed markedly from that of the cells of the bronchial origin. In addition, cells of alveolar origin were frequently phagocytic after they had assumed a typical epithelium-like structure and arrangement. Although no conclusions were drawn regarding the entodermal or mesenchymal nature of the lining cells of the alveoli origin, it was conjectured that their parent cells also gave rise to the alveolar phagocytes. *Pulmonary alveoli linings in bronchiectasis, C. F. Watts & J. R. McDonald, Arch. Path., June, 1948, 45: 742.*—(*E. Bogen*)

Pulmonary Emphysema.—Pulmonary emphysema is difficult to diagnose by physical and roentgenologic examination. With the appearance of dyspnea and fatigue in chronic pulmonary or cardiac disease, a diagnosis of emphysema is frequently improperly made. Inasmuch as pulmonary emphysema is a functional disease due to interference with the interchange of oxygen and carbon dioxide between the alveolar air and the blood, a diffusion test designed to measure the efficiency of this interchange can confirm or rule out emphysema of the lung. Without this diffusion test it is most difficult to state whether or not emphysema of the lung is present even when severe dyspnea exists. Dyspnea most frequently is caused by marked reduction in pulmonary ventilatory function. Several documented case records are reported to demonstrate that marked reduction in pulmonary ventilation can exist and emphysema of the lung not be present. Overdistention of a lung can exist for a long time without the development of pulmonary emphysema. A lung may hypertrophy and remain so for many years without loss of ventilation or diffusion functions. An hypertrophied lung may increase its ventilatory function through having been hypertrophied and overdistended for many years. The presence of emphysematous blebs or bullae in the lungs does not necessarily imply that the lungs are emphysematous unless there is functional impairment of pulmonary diffusion of oxygen and carbon dioxide. (Author's Summary)—*A new approach to the understanding of pulmonary emphysema: A method of determining emphysema of the lungs, G. G. Ornstein, Quart. Bull., Sea View Hosp., April, 1947, 9: 89.*—(*K. T. Bird*)

Bullous Emphysema with Infection.—Apparent cavitation was demonstrable on chest roentgenograms in 12 of 20 cases of primary atypical pneumonia seen during 1947. Two patients developed foul sputum for a short period and in 2 an atypical pulmonary abscess occurred. In 2 other cases the diagnosis of lung abscess was based on roentgenologic evidence of rarefaction, although the patients had no fever and no sputum. In all cases there was only a mild reaction about the cavities. It seemed unlikely that these were instances of ordinary lung abscess with dissolution and excavation of parenchymal tissue. However, an incomplete blocking of the bronchial branches by exudate or inflammatory changes

during primary atypical pneumonia may give rise to emphysematous bullae which resemble rarefaction in the chest roentgenogram. Superimposed anaerobic infection of these bullae may occur with the development of the clinical picture of putrid lung abscess.—*Development of putrid pulmonary abscess in emphysema-bladders in primary atypic pneumonia, M. Ch. Ehrstrom, Acta med. Scandinav., 1948, 129: 573.*—(*K. T. Bird*)

Acute Lung Abscess.—The treatment of acute abscess of the lung by postural drainage, transthoracic injection of sulfonamides and penicillin, bronchoscopic aspiration, endobronchial catheterization, and nebulization offers a maximum of 30 per cent cures with a high mortality from residual bronchiectasis and fibrosis. The tendency of the process to spread and its marked toxicity demand early surgical external drainage. Four cases of acute lung abscess have been treated by external minimal drainage, intracavitary aspiration, and penicillin. This was given by concomitant instillation into the cavity and by intramuscular injection. The technique employed was: (*1*) aspiration of pus from the abscess under fluoroscopic control; (*2*) lipiodol injection into the cavity to outline its inferior limits; (*3*) roentgenography; (*4*) drainage under local anesthesia using a 0.5 cm. incision and introducing the trocar of a Coryllos thoracoscope through a thin layer of relatively avascular pulmonary tissue; (*5*) passage through the trocar of a flexible catheter which was secured to the chest wall; (*6*) continuous aspiration for 48 hours and then intermittent suction, alternating with injections through the catheter of 100,000 units of penicillin every 24 hours for five to ten days. Intramuscular penicillin, sulfonamides, liver, and vitamin C were also administered. Roentgenograms were taken every 48 hours. The aspirations were discontinued if they produced a hemorrhagic discharge or if the secretions disappeared with the loss of a fluid level and reduction in the size of the cavity.—*Tratamiento del absceso agudo del pulmón por drenaje externo a mínima, con aspiración endocavitaria, J. M. Casal, Rev. de tuberc., d. Uruguay, March, 1948, 16: 24.*—(*F. Pérez-Pina*)

Putrid Lung Abscess.—At the Harlem Hospital in New York City, spontaneous recovery from acute putrid abscess of the lung has been noted only in 11 per cent of 70 patients. Twenty-one patients with the acute disease have been treated with penicillin and sulfadiazine. Sulfadiazine alone has been found to be ineffective but it was hoped that it would act synergistically with penicillin, particularly against the perifocal pneumonitis. The sodium salt of penicillin was administered intramuscularly in doses of 40,000 units every three hours. The dose was increased if a prompt response was not obtained and several patients required 100,000 units every three hours. Sulfadiazine was given orally in the usual doses. Therapy was continued until all clinical and roentgenologic evidence of disease had disappeared. Nineteen of the 21 patients recovered completely. One patient died of a brain abscess although the pulmonary disease was cured; one patient left the hospital before treatment was completed. The average curation of treatment required to produce a remission of distressing symptoms and fever was six days (range from 2 to 35 days). An average of 42 days (range from 18 to 78 days) of treatment elapsed before the roentgenograms appeared normal. There were two recurrences, one in a severe epileptic and one in a severely alcoholic patient. The therapy was equally effective for small or large cavities and the authors believe that the size of the cavity is primarily determined by the degree of local obstructive emphysema rather than tissue necrosis. This type of treatment does not cure chronic putrid lung abscesses but in 8 of 10 patients the disease was improved and they were considered better candidates for surgical therapy. In view of the results obtained with drug therapy, the practice of early surgical drainage of acute putrid lung abscess must be revised.—*The treatment of acute putrid lung abscess with penicillin and sulfadiazine, B. P. Stivelman*

and J. Kavee, Ann. Int. Med., February, 1949, 30: 348.—(H. H. Nayer)

Endothelioma of the Pleura.—The clinical features and the differential diagnoses of 10 cases of endothelioma of the pleura are discussed. The average age was 50 years, and death usually occurred within four to six months. The most important clinical sign is the rapid development of a hemorrhagic exudate which shows a marked tendency to reform after drainage. The strain on the pulmonary circulation always causes right ventricular hypertrophy with dilatation and corresponding electrocardiographic changes. Pronounced dyspnea develops; a secondary hypochromic anemia occurs regularly, and the sedimentation rate is increased. The Weltmann reaction shows a shift to the left.(Author's Summary)—*Zur Klinik der sogenannten Pleuraendotheliome (Mesotheliome), X. Kaiser, Schweiz. Ztschr. Tuberk., 1948, no. 4: 189.—(E. Dunner)*

Pulmonary Adenomatosis.—Pulmonary adenomatosis represents about 5 per cent of all lung tumors, occurring in women more frequently than in men (ratio 3:2). The human disease resembles morphologically the pulmonary adenomatosis of sheep (Jagsiekte) which is thought to be caused by a filterable virus. Efforts to isolate a virus from the human cases have not been successful; the evidence seems to indicate that this disease is a specific response to certain nonspecific irritants. This response is hyperplastic and eventually causes death by extensive involvement of the lung parenchyma or by the development of truly malignant properties. Grossly pulmonary adenomatosis usually resembles the stage of gray hepatization in pneumonia. Nodular, consolidated areas, somewhat like noncaseating miliary tuberculosis, have been described also. A primary bronchial focus has never been demonstrated. Nonciliated cuboidal or columnar cells line the alveolar walls which are otherwise unaffected. The cytoplasm of these cells is eosinophilic, granular, or somewhat foamy. Bronchopneumonia often obscures the condition. Although microscopically identical with so-called "alveolar cell carcinoma," pulmonary adenomatosis differs from carcinoma in that it usually does not metastasize. Two cases of extension have been reported, however, and metastasis has occurred in Jagsiekte of sheep. It is likely that adenomatosis of the lungs is a relatively benign variant of the "alveolar cell carcinoma" and is capable of developing all the characteristics of malignancy. There are no distinguishing clinical features of pulmonary adenomatosis. Each of the authors' 3 cases presented unusual findings. The findings in one case suggest a bronchogenic origin for the disease. In another case there was malignant proliferation of the cells of the adenomatous process. The nature of the cuboidal epithelium lining the air sacs and the loss of normal pulmonary architecture are unusual variations of the disease in the third case.—*Pulmonary adenomatosis: A report of three cases, G. W. Drymalski, J. R. Thompson, & H. C. Sweany, Am. J. Path., September, 1948, 24: 1083.—(J. S. Woolley)*

Cytological Examination of Sputum.—Sputum specimens of 1,600 patients were examined cytologically for cancer cells by the method of Dudgeon and Wrigley. Positive results were obtained in 150 cases. Normal and abnormal cells are described in detail. Statistically, examination of the bronchial secretions was no better than that of the sputum; however, examination of one supplemented the other. Of the 150 cases with positive findings, a final diagnosis of cancer was made in 145. In 3, the suspected condition was found to be noncancerous. In the other 2, the diagnosis of cancer was suspected but not proved. Bronchoscopy was performed for 114 of these cases. Positive biopsies were obtained in 66, negative biopsies in 31, and no gross abnormalities were seen in 17. In the other 32 proved cases of cancer, bronchoscopy was not done, the diagnosis having been proved in other ways. Surgery was done in 58 cases including 31 with a positive and 25 with a negative bronchus biopsy. The con-

dition was operable in 24, including 15 with positive and 9 with negative biopsies.—*Carcinoma cells in sputum and bronchial secretions, L. B. Woolner & J. R. McDonald, Surg., Gynec. & Obst., March, 1949, 88: 273.*—(*A. G. Cohen*)

Antimicrobial Therapy

Para-aminosalicylic Acid.—Para-aminosalicylic acid (PAS) was discovered in the course of investigations of the metabolism and growth of tubercle bacilli. In 1940 and 1941, Bernheim showed that salicylic and benzoic acid increase the oxygen utilization and carbon dioxide formation of tubercle bacilli. Salicylic acid exerts this action only on pathogenic tubercle bacilli and is thought to act as a co-factor in the oxidative process. Lehman obtained identical results and noticed that salicylic acid exerts a powerful bacteriostatic action on tubercle bacilli in synthetic media. In an attempt to find a compound that competes with salicylic acid in the oxidative processes of tubercle bacilli, he investigated 60 derivatives of salicylic and benzoic acid. Para-aminosalicylic acid showed tuberculostatic activity which is equalled by few compounds and approaches the activity of streptomycin, inhibiting virulent human tubercle bacilli in a concentration of 1:2,000,000. The effectiveness of PAS in the treatment of experimental tuberculosis was quickly proved and it was found that the drug had a low toxicity. Clinical investigations established the dosage as 10 to 15 Gm. daily in divided doses given over a period of months, one week of treatment alternating with one week without treatment. More than 100 patients with pulmonary tuberculosis were treated; 60 to 70 per cent showed good result initially. Results also are promising in renal tuberculosis and in the topical treatment of abscesses and empyema cavities with a 10 per cent solution of PAS or its sodium salt. The drug has not fulfilled its promise, however, in the treatment of miliary tuberculosis and tuberculous meningitis, perhaps because insufficient doses have been used.—*P-Aminosalicylsaüre in der Chemotherapie der Tuberkulose, L. Ragaz, Schweiz. med. Wchnschr., April 10, 1948, 78: 332.*—(*H. Marcus*)

PAS for Tuberculosis.—A total of 30 cases of tuberculosis were treated with para-aminosalicylic acid (PAS). The drug was administered orally for four days followed by a three day pause. The treatment was continued over a period of several months, the daily dose averaging 12 to 15 Gm. Definite beneficial effects on temperature elevation, amount of sputum, number of tubercle bacilli, and sedimentation rate were observed especially in the exudative forms. In 5 cases of tuberculous empyema complicating intra- or extrapleural pneumothorax, PAS was used locally. After several weeks of treatment, growth of tubercle bacilli on culture was inhibited in each case.—*Die Behandlung der Tuberkulose mit Para Amino Salicylsaüre, H. Steinlin, Schweiz. Ztschr. Tuberk., 1948, no. 6: 391.*—(*E. Dunner*)

Para-aminosalicylic Acid for Tuberculosis.—Para-aminosalicylic Acid (PAS) and sodium PAS are being used extensively in Switzerland for chronic pulmonary tuberculosis with cavities and for tuberculosis of the bronchi, larynx, cervical nodes, urinary tract, and middle ear. It also is used intrapleurally for empyema. The drug is introduced directly into the cavity in daily doses of 2 cc. of a 20 per cent solution. This is supplemented by 10 to 20 Gm. daily given orally in divided doses. For bronchial lesions, 2 cc. of 20 per cent solution are administered as aerosol, supplemented by 10 Gm. daily by mouth. For otitis media, 2 to 3 drops of 20 per cent solution are used. In renal disease, 10 to 20 Gm. are given orally each day. The drug is available in ointment and cream for use in external sinuses and ulcers. Sometimes sodium PAS is given intravenously. PAS also is used in conjunction with streptomycin.—*PAS in Switzerland, M. Seiler, Tubercle, February, 1949, 30: 45.*—(*A. G. Cohen*)

Lupus Vulgaris.—The treatment of cutaneous tuberculosis with calciferol frequently

leaves the patient with residual activity in the lesions. Five patients with lupus vulgaris were treated with calciferol until it ceased to be of benefit after a period of five months to a year. They were then treated with streptomycin in combination with calciferol. The lesions became inactive within six to nine weeks, suggesting a synergistic action of the 2 drugs. Two other patients were treated with streptomycin and calciferol for seven and eight weeks, respectively. They received 1.0 Gm. of streptomycin and 100,000 units of calciferol daily. Both patients showed rapid and uneventful healing of the lesions.—*Combined calciferol and streptomycin in lupus vulgaris, T. Cornbleet, J. A. M. A., December 18, 1948, 138: 1150.—(H. Abeles)*

Streptomycin Frugality.—Experience with penicillin and a consideration of Corper's conclusions from the use of streptomycin in animals have resulted in a program for treating certain types of tuberculosis in children. Smaller doses and less frequent injections than have ordinarily been prescribed are used. Treatment is given without interruption until the lesions are stable; the doses being reduced and the intervals increased as treatment progresses. It has been found that a solution containing 166 mg. per cc. can be used with comfort. A series of cases is reported in which such a routine was used. All of 13 cases were acute and febrile before treatment; 3 had miliary disease, 6 had hilus gland lesions, and 4 had primary childhood type of tuberculosis. The miliary cases were treated for two to four months and the others from four to six weeks. At the start 20 mg. per Kg. of body weight per day were given at intervals of four hours; the dose was decreased to 5 mg. per Kg. per day and the interval lengthened to twelve hours or even 48 to 72 hours in some cases by the end of the second week. All cases healed. A case is reported in detail to demonstrate the repeatedly unfavorable effects of discontinuous administration.—*Streptomycin in tuberculosis of children: Treatment with less frequent injections and more concentrated solutions, D. Hirschl, H. Levy & A. M. Litvak, Arch. Pediat., December, 1948. 65: 640.—(W. H. Oatway, Jr.)*

Antihistaminic Drugs with Streptomycin.—Nausea and vomiting occur in some patients undergoing prolonged treatment with streptomycin and might be due to the same cause as the urticaria sometimes seen. In 4 patients severe toxic symptoms were abolished or considerably reduced when benadryl was given and returned when the medication was withheld. This response might have been due to the sedative effect of benadryl but, when 30 mg. of phenobarbital was substituted, the nausea returned. The resumption of benadryl was followed by immediate relief. In 3 of the 4 cases, the nausea and vomiting were so severe that streptomycin therapy would have been discontinued but for the beneficial effect of benadryl in relieving the symptoms.—*Antihistamine drugs in treatment of nausea and vomiting due to streptomycin, J. R. Bignall & J. Crofton, Brit. M. J., January 1, 1949, no. 4591: 13.—(R. W. Clarke)*

Vitamin B Deficiency with Streptomycin.—Three patients who were receiving streptomycin for tuberculosis developed angular stomatitis and glossitis. These were relieved by the administration of niacin and ribroflavin. Neither 15 other patients currently on the ward nor 154 patients treated during the year showed similar findings. Evidence is presented to show that streptomycin exerts a bacteriostatic effect on intestinal organisms which may be concerned in the assimilation of these vitamins.—*A clinical report of three cases of vitamin B deficiency occurring during streptomycin therapy, J. Sumner, Tubercle, March, 1949, 30: 62.—(A. G. Cohen)*

Streptomycin for Pertussis.—Because strains of *H. pertussis* were found to be sensitive to streptomycin *in vitro*, it was thought desirable to ascertain the efficacy of the drug in the treatment of whooping cough. A total of 11 children were treated. In 3 cases, two daily treatments were given consisting of inhalation of 50,000 units of nebulized streptomycin by means of a special helmet.

In 3 cases, the treatments were given four times a day. In 3 cases, 200,000 units were given intramuscularly four times a day. In one case, both intramuscular and inhalation treatments were given. Streptomycin was not recovered from the blood or urine of any patient who received the drug by inhalation alone. The clinical course of the disease was not modified in any treated case.—*Streptomycin in whooping cough, H. Schwabacher, R. H. Wilinson & C. W. C. Karran, Lancet, January 29, 1949, 2: 180.*—(*A. G. Cohen*)

Streptomycin for Pneumonia.—Respiratory infections may be caused by *Hemophilus influenzae* and in infants there are no typical clinical characteristics of the disease. Mortality in infants has ranged from 7 to 40 per cent, depending on what part of the respiratory tract is involved, despite the use of sulfonamides and antiserum. Three cases with a laryngotracheitis due to *H. influenzae* were treated with streptomycin; all improved abruptly within twelve hours. Four cases of laryngotracheobronchitis due to the organism were treated with streptomycin; they improved within twelve hours and all recovered. No streptomycin-resistant strains were found. It is suggested that the drug be given to all young infants with laryngotracheobronchitis and continued until a nonsusceptible organism has been demonstrated.—*Streptomycin in the treatment of Hemophilus influenzae laryngotracheobronchitis, C. O. Terrell Jr. & C. S. Hoar, J. Pediat., February 1949, 34: 139.*—(*W. H. Oatway, Jr.*)

Empyema.—The extensive use of penicillin in infections of the respiratory tract has reduced the frequency of pleural abscesses to 0.08 per cent or less in most series of cases. If pleural fluid appears, local treatment should be withheld until an attempt has been made to identify the infecting organisms. Penicillinase should be used in the laboratory to counteract the inhibitory effect of penicillin on the organisms if the agent already has been given. Streptomycin should not be employed unless there are absolute indications based on bacteriologic evidence. The early, vigorous, parenteral, and intrapleural use of penicillin as soon as infected fluid appears in the pleura will abort the formation of a frank abscess in many cases. If frank, thick pus forms, however, surgical drainage or decortication with drainage should be employed.—*Empyema, B. Blades, J. A. M. A., November 27, 1948, 138: 943.*—(*H. Abeles*)

Aureomycin for Atypical Pneumonia.—Thirteen patients with primary, atypical, nonbacterial pneumonia were treated with aureomycin. Detailed data of the clinical, laboratory, and serologic findings are given. Six patients had high titers of cold hemagglutinins and 9 patients had positive *Streptococcus MG* agglutination reactions. Treatment with aureomycin was begun on the second to twenty-first day of illness. The usual schedule of drug administration consisted of a "priming" dose of 100 to 250 mg. every hour for 3 doses, followed by the same dosage every two hours until the patient became afebrile. Thereafter, the drug was given every four to six hours for two to five days (15 to 20 mg. per Kg. of body weight). Nine patients were afebrile within 24 hours after the institution of aureomycin therapy, 3 within 24 to 48 hours, while one patient did not become afebrile until 72 hours after treatment. Subjective clinical improvement coincided with lysis of the fever. There were no serious toxic manifestations although several patients complained of mild drowsiness.—*Treatment of primary atypical nonbacterial pneumonia with aureomycin, E. B. Schoenbach & M. S. Bryer, J. A. M. A., January 29, 1949, 139: 275.*—(*H. Abeles*)

Laboratory Studies

Pleural Fluid Sugar.—The sugar content of the pleural fluid was determined in a series of 33 cases, the venous blood sugar being determined at the same time. The results suggest that a low concentration of sugar in the pleural fluid may be diagnostic of tuberculosis. Each of the 10 cases of tuberculosis had a sugar concentration below 39.5 mg. per 100 cc., the average being 15.7 mg. It is felt that the finding of 30 mg. per 100 cc. or less should be diagnostic of tuberculosis while a concentration above 60 mg. per 100 cc. should eliminate

tuberculosis as the cause of the effusion.—*Relationship of the pleural fluid sugar to pulmonary tuberculosis, S. M. Gelenger & R. F. Wiggers, Dis. of Chest, March, 1949, 15: 325.*—(*E. A. Rouff*)

White Mouse in Tuberculosis.—The white mouse is extremely useful in experimental tuberculosis. Following intravenous injection of a standardized inoculum of tubercle bacilli, the severity of the infection can be measured by the length of the survival time and the extent of macroscopic dissemination. With this method doses of 0.06 to 1.0 mg. of virulent tubercle bacilli yield easily reproducible results in full-grown mice. They die within three weeks. Both sexes appear equally susceptible but the infection has a more irregular and prolonged course in immature mice. The size of the animal, the simplicity of the intravenous technique of infection, and the small amounts of drugs that are required for therapeutic evaluation facilitate extensive experimental investigations. The only obvious disadvantage is the marked susceptibility of the white mouse to intercurrent infections, particularly those with the Salmonella group of bacilli.—*The white mouse in experimental tuberculosis, B. Swedberg, Acta tuberc. Scandinav., 1948, 22: 260.*—(*K. T. Bird*)

Bacillary Wax and Delayed Hypersensitivity.—Studies of delayed hypersensitivity to tuberculin have demonstrated that: (*1*) the isolated protein antigen of the tubercle bacillus cannot induce tuberculin hypersensitivity but the entire organism can; (*2*) the "wax" of the bacillus when administered with protein causes a delayed response. Picryl chloride alone induces delayed hypersensitivity only when administered through the skin but, if tubercle bacilli are injected with picryl chloride by another route, delayed hypersensitivity to the chemical ensues. Picryl chloride is a simple hapten which combines spontaneously with protein to form a complete antigen in the tissues. The "wax" of the tubercle bacillus may determine the delayed response to picryl chloride as it determines the similar response to tuberculoprotein. To test this thesis, groups of guinea pigs were treated with picryl chloride by applying it to the skin or by injecting it intracutaneously, subcutaneously, and intraperitoneally. The chemical was injected intraperitoneally with a water in oil emulsion or with the "wax" from tubercle bacilli. All animals later received both contact and intracutaneous skin tests with weak solutions of picryl chloride. A few animals, especially those sensitized by placing the chemical on or into the skin, later reacted moderately to the contact and intradermal tests. Thirteen of the 15 animals which received picryl chloride with "wax" developed marked delayed hypersensitivity to both tests after only one treatment. This sensitivity was not increased by repeated injections and it persisted for 164 days. The high degree of hypersensitivity appears to depend upon a specific property of the "wax"; a simple adjuvant activity is unlikely because the water in oil emulsion did not cause the same responsiveness to the antigen. Further tests showed that the reaction bore no relationship either to the occurrence of a humoral antibody or to an immediate hypersensitivity of the anaphylactic or Arthus type. Passive transfer of the hypersensitivity was impossible. The so-called "heteroallergic" phenomena in tuberculosis may appear because the bacillary "wax" causes tissues to respond with tuberculin-type reactions to various antigenic substances. The moderate, delayed response to picryl chloride introduced along by way of the skin, may be due to a tissue lipid with properties similar to those of the bacillary "wax".—*The role of the "wax" of the tubercle bacillus in establishing delayed hypersensitivity: I. Hypersensitivity to a simple chemical substance, picryl chloride, S. Raffel & J. E. Forney, J. Exper. Med., October 1, 1948, 88: 485.*—(*J. S. Woolley*)

Virulence Variations of BCG.—Four strains of BCG which had been cultivated differently for many years were studied under standardized conditions. It was found that the virulence of these strains was rather uniform regardless of whether they had been cultivated exclusively on bile-potato medium, on bile-potato medium and glycerine-potato medium

alternately, or exclusively on Sauton's medium. For some BCG strains at least, it is apparently immaterial whether they are maintained on a medium containing bile. Some of the variation in the action of BCG may be due to differences in the technique of preparing the vaccine rather than to changes in virulence. The rate of growth of a culture and the stage of growth at which it is collected are significant factors in this respect. Because a standardized technique is so important, an international BCG standard would be helpful. Preliminary studies of BCG vaccine with a freeze-drying technique give promise of a basis for the latter.—*Variations in the Virulence of BCG, J. Bée, Acta tuberc. Scandinav., 1948, 22: 125.*—(*K. T. Bird*)

Rapid Streptomycin Sensitivity Test.—The usual methods of determining the streptomycin sensitivity of tubercle bacilli make results available to the clinician only after six to eight weeks. A more rapid technique has been elaborated in the Institute of Hygiene, Lausanne, Switzerland. A part of each specimen is mixed with an equal amount of a streptomycin solution containing either 1.0 or 10γ per cc. These mixtures are inoculated directly on solid Lowenstein medium. Three series of tubes are incubated: (*1*) specimen without streptomycin; (*2*) specimen with streptomycin solution of 1.0 γ per cc; (*3*) specimen with streptomycin solution of 10 γ per cc. The results can be evaluated after two weeks. The strain is considered resistant if it grows in both streptomycin dilutions. A strain is considered at the lower limit of resistance if it grows only in 1.0 γ per cc. This method admittedly gives only a rough estimate of the streptomycin sensitivity and should always be followed by the usual sensitivity determinations in liquid media.—*Nouvelle méthode de titration de la streptomycino-résistance du bacille tuberculeux, P. Haduroy et W. Rosset, Rev. de la tuberc., 1948, 12: 834.*—(*V. Leites*)

Plastic Irritants.—Certain synthetic plastic materials have the ability to incite fibrosis. Cellophane and polythene are such irritants although the effect of the latter varies with its quality. The experimental production of pleural and pulmonary fibrosis has been tried in a dozen dogs using the two plastics. A sheet of plastic was wrapped around portions of one lung at pleurotomy after which the effects were noted clinically at the end of three and six months. Both plastics produced thickened pleura, collapse of the chest wall and lung, and some fibrosis of the lung. Cellophane tends to produce a fulminating type of reaction but the changes are compatible with life and health. The effect of the films was variable, since the reaction is due to plasticizers used in manufacture and the film is the vehicle of the chemical on its surface. The utility and effect of the methods in human tuberculosis is conjectural but it could be tried for the production of adhesions and to obliterate blebs and fistulae.—*Experimental pulmonary collapse, J. L. Southworth, Ann. Surg., January, 1949, 129: 85.*—(*W. H. Oatway, Jr.*)

Tissue Distribution of PAS.—The distribution of para-aminosalicylic acid (PAS) in various tissues was studied by means of fluorescence microscopy. Specimens were fixed in liquid air and dried *in vacuo* before being embedded in paraffin and sectioned. No staining was performed. In ultra violet light PAS has a strong, green fluorescence. It was found that PAS accumulates in elastic fibres but not in collagenous tissue so that a normal lung absorbs relatively large quantities of this drug. However, the quantities are smaller in tuberculous cavities where the elastic fibres are severed and partially destroyed.—*The distribution of para-aminosalicylic acid in the tissues, K. Alin & S. Helander, Acta tuberc. Scandinav., 1948, 22: 283.*—(*K. T. Bird*)

Insulin Tolerance in Amyloidosis.—The insulin tolerance test is shown to be abnormal in amyloidosis. This abnormality consists of an increased resistance to insulin and an impaired response to hypoglycemia. It is suspected that this response is the result of hepatic dysfunction. The cases studied also showed an abnormal retention of bromsulfalein and significantly positive cephalin-

cholesterol flocculation tests in addition to Congo red absorption and hepatomegaly. The test responses were similar to those found in other types of liver disease and to those elicited in cases of portal cirrhosis tested concurrently. (Author's Summary)—*The insulin tolerance test in amyloidosis, S. London, Quart. Bull., Sea View Hosp., April, 1947, 9: 187.*—(*K. T. Bird*)

Public Health and Epidemiology

Loss of Tuberculin Sensitivity.—A series of 7,500 school children from 4 to 20 years of age was tested with tuberculin. Children under 14 were tested by percutaneous methods; the intracutaneous method was used for older subjects. All were observed for periods of one to seven years, 2 to 10 tests being made in each case. When the reactions became negative, control tests were made eight to fifteen days later. Of the7, 500 children, 2,315 showed positive reactions when first tested; 320 of them later became negative reactors. Of 496 children 4 to 10 years of age, 175 (35 per cent) became negative reactors; of the 1,338 children 11 to 15 years of age, only 128 (9.5 per cent) failed on subsequent tests to react to tuberculin. Of the 441 students 16 to 20 years old, 17 (3.8 per cent) became nonreactors. Attention is called to the fact that young children often have been removed from foci of infection. Acute tuberculosis is less frequent among them than among adolescents who are more exposed to reinfection. Reappearance of sensitivity to tuberculin after it has been lost is considered by the authors to be evidence of reinfection rather than of the persistent influence of primary infection.—*Extinction spontanée des réactions cutanées à la tuberculine chez l'homme, M. Gillard & A. LeCocq, Acta tuberculosea Belgica, April, 1948, 39: 97.*—(*A. T. Laird*)

Effect of Amount of Tuberculin.—A series of 109 apparently healthy individuals were subjected to 2 simultaneous Mantoux tests. Of the individuals, 94 had normal chest roentgenograms, 3 showed hilar adenopathy, and 9 had pulmonary calcifications. Each subject received 0.1 cc. of a 1:5,000 tuberculin solution at one site and 0.2 cc. of the same dilution at a second site 10 cm. away from the first. There was a negative reaction to the 0.1 cc. injection in 33 per cent of the subjects and a negative reaction to the 0.2 cc. injection in only 19 per cent. The positive reactions were generally stronger with the larger injections. Similar tests were conducted on 110 individuals using 0.1 cc. of a 1:5,000 tuberculin solution and 0.2 cc. of a 1:10,000 solution. The reactions obtained with these two injections were almost identical. Thus the amount of tuberculin rather than the volume of solution injected determines the results obtained. *Contribución a la práctica de la reacción de Mantoux, A. R. Ginés, E. Gould, & C. R. Talavera, Hoja tisiol., June, 1948, 8: 117.*—(*F. Pérez-Pina*)

BCG in Adults.—The authors have administered BCG by the scarification route to 4 different groups of student nurses in Paris since 1942. In the first group 100 tuberculin-negative student nurses have been vaccinated since 1942. One of them developed serofibrinous pleurisy eighteen months after vaccination but recovered without further consequences. All of the other students have remained in perfect health. Some nonreactors in the same group refused vaccination. In 38 per cent of them, tuberculous manifestations have appeared, including erythema nodosum, serofibrinous pleurisy, tuberculous peritonitis, and active pulmonary tuberculosis. In a second group of nurses, 43 nonreactors have received BCG since 1943. None of them has developed any tuberculous manifestations during the following five years, whereas in the years preceding the use of BCG one case of miliary tuberculosis and 6 cases of primary tuberculosis had been observed. In a third group of student nurses, 50 have been vaccinated since 1944. Among them there has been one case of abscess due to BCG and this healed spontaneously. No other tuberculous incidents have been noted. A fourth group of student nurses have received BCG since 1945. Among the vaccinated persons there were 3 cases of transient mediastinal adenopathy with fever. From 1939 to 1945, before the use

of BCG, 21 of 116 nonreactors developed tuberculous manifestations, 3 of which were fatal.—*L'extension de la prévention de la tuberculose par le BCG aux adolescents et adultes, A. Courcoux, Presse med., June 12, 1948, 410.*—(V. Leites)

Contact Control During Vaccination.—An individual is "vaccinated" with BCG only when a routine is observed which protects him from contact infection until the inoculation becomes effective. Proof of "vaccination" can be obtained only by the use of pre- and post-inoculation tuberculin tests. There is a definite difference between the terms "BCG inoculation" and "BCG vaccination"; the inoculated individual must have had the required tuberculin tests to be considered vaccinated and to be usable in statistics. The report of Levine and Sackett of New York is vulnerable because of a failure to isolate infants during the inoculation period. They were aware of this fault, as shown by their follow-up study, but their objection to isolation is not valid. When isolation and control are used, the results show an eminent advantage. Control groups of unvaccinated persons are no longer available in Sweden since physicians consider it a dangerous experiment to withhold BCG inoculation and the law considers it criminal.—*BCG inoculation and BCG vaccination, A. Wallgren, Am. J. Dis. Child., November, 1948, 76: 485.*—(*W. H. Oatway, Jr.*)

Q Fever.—Q fever was first recognized in California in April, 1947. This study includes 300 cases that have been investigated in the Los Angeles area since September, 1947. A definite diagnosis was made either on the basis of recovery of *C. burneti* from the tissues in two fatal cases, from the blood of other acutely ill patients and the urine of convalescents, or on the basis of the complement fixation test. A total of 483 complement fixation tests were made; in general, the titers increased until the fourth week of illness and then tended to subside gradually over a period of years. Pneumonia was the initial diagnosis by physicians in over 100 cases and was noted in the roentgenograms of 97 of 115 cases. Chest pain, cough, and hemoptysis were described. The cases occurred throughout a wide area at all seasons and over several years. The patients were predominantly males in the industrial age groups but their occupations were extremely diversified. In all, the epidemiological findings suggested 3 general hypotheses as to the modes of spread: (*1*) occupation in the dairy or livestock industries; (*2*) residence close to dairies or livestock yards; and (*3*) household use of raw milk. *C. burneti* was recovered from 40 of 50 specimens of raw milk collected from five dairies. However no one of these possible modes of spread would account for more than one-half of the cases.—*Q Fever studies in Southern California: II. An epidemiological study of 300 cases, M. Beck, J. Bell, E. Shaw, & R. Huebner, Pub. Health Rep. January 14, 1949, 64: 41.*—(*S. Hadley*)

Industrial Atmospheric Pollution.—Donora is a borough in Pennsylvania inhabited by 14,000 people. Its main industries are a zinc smelting plant, a steel and wire plant, and slag crushing plants. It is situated on a river along whose banks many heavy industries are located. There is very heavy river and rail traffic which adds to the pollution of the air. For four days last winter there was an exceptionally heavy fog. The following day deaths began to occur rapidly, reaching a total of 18 in 36 hours. All the victims were known to have had heart disease or asthma; their ages ranged from 52 to 85 years. Five hundred other people suffered from dyspnea and cough. On the second day, repeated samples of air were analyzed for sulphur dioxide, which is the most irritating of industrial gases. The first sample showed 0.54 parts per million, falling to 0.08 parts in five hours, at about which time the disaster began to abate. The situation on the previous day unfortunately is not known. The upper limit of safety for sulphur dioxide is thought to be 0.5 to 0.75 parts per million. These concentrations were approached, if not exceeded. Soluble sulfates were found to be present in a concentration of 0.2 mg. per cubic meter.—*The Donora disaster, J. Shillen, Indust. Med., February, 1949, 18: 70.*—(*A. G. Cohen*)

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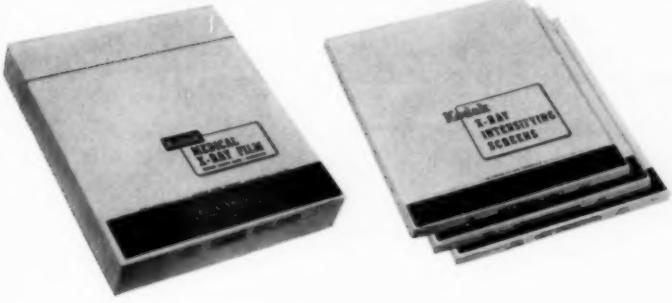

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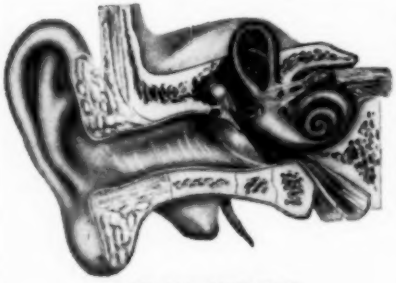

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